Search Strategy

FILE 'USPATFULL' ENTERED AT 08:59:02 ON 16 NOV 2000

		E	DEACON NICHOLAS J/IN
L1	3	S	E3 OR E4
		E	CATHERINE JENNIFER/IN
		E	LEARMONT JENNIFER/IN
L2	1	S	E4
		E	MCPHEE DALE/IN
L3	3	S	E4
		E	CROWE SUZANNE/IN
L4	2	S	E3
		E	COOPER DAVID/IN
L5	24	S	E3
L6	11252	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L7	269	S	L6 AND (NEF OR NEGATIVE FACTOR OR NEGATIVE REGULATORY FACTOR)
L8	230	S	L7 AND (VACCINE OR THERAPEUTIC)
L9	96	S	L8 AND (ATTENUAT? OR NON-PATHOGENIC OR LESS PATHOGENIC OR LES
L10	73	S	L9 AND (HIV/CLM OR HUMAN/CLM)
L11	45	S	L7 AND NEF/CLM
L12	32	S	L11 NOT L10

FILE 'WPIDS' ENTERED AT 09:22:54 ON 16 NOV 2000

		E	DEACON NICHOLAS J/IN
L13	3	S	E2
		E	LEARMONT J C/IN
L14	1	S	E3
		E	MCPHEE D A/IN
L15	4	S	E3
		E	CROWE S/IN
L16	5	S	E3
		E	COOPER D/IN
L17	45	S	E3
L18	1	S	L17 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR NEF OR NEGATI
L19	7922	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L20	74	S	L19 AND (NEF OR NEGATIVE FACTOR OR NEGATIVE REGULATORY FACTOR
L21	39	S	L20 AND (VACCINE OR THERAPEUTIC)
L22	9	S	L21 AND (ATTENUAT? OR NON-PATHOGENIC OR LESS PATHOGENIC OR LE
L23	7	S	L22 NOT L13

FILE 'AIDSLINE' ENTERED AT 09:33:01 ON 16 NOV 2000

		E	DEACON N J/AU
L24	70	S	E2 OR E3
L25	22	S	L24 AND (NEF OR NEGATIVE FACTOR OR NEGATIVE REGULATORY FACTOR
		E	LEARMONT J/AU
L26	50	S	E3 OR E4
L27	44	S	L26 NOT L25
L28	43	S	L27 AND (HIV OR NEF)
		E	MCPHEE D/AU
L29	80	S	E3 OR E4
L30	80	S	L29 AND (HIV OR NEF)
L31	61	S	L30 NOT L24
L32	56	S	L31 NOT L26
		E	CROWE S/AU
L33	59	S	E3

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L34          51 S L33 NOT (L24 OR L26 OR L29)
L35          50 S L34 AND (HIV OR NEF)
                E COOPER D/AU
L36          94 S E3
L37          90 S L36 NOT (L24 OR L26 OR L29 OR L33)
L38          79 S L37 AND (HIV OR NEF)
L39           0 S L38 AND NEF
L40           0 S L38 AND (LTNP OR LONG-TERM NON-PROGRESSOR?)
                E DESROSIERS R/AU
L41         196 S E3 OR E4
L42          58 S L41 AND (NEF OR NEGATIVE FACTOR OR NEGATIVE REGULATORY FACTOR
L43          20 S L42 AND (ATTENUAT? OR NON-PATHOGENIC OR LESS PATHOGENIC OR AV
L44          13 S L42 AND VACCINE
L45           1 S L44 NOT L43
L46          38 S L42 NOT L43
                E RUPRECHT R/AU
L47          67 S E3 OR E4
L48          14 S L47 AND NEF
L49      138207 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L50        1536 S L49 AND (NEF OR NEGATIVE FACTOR OR NEGATIVE REGULATORY FACTOR
L51         163 S L50 AND VACCINE
L52          57 S L51 AND (ATTENUAT? OR NON-PATHOGENIC OR LESS PATHOGENIC OR AV
L53          46 S L52 NOT (L47 OR L41)
L54           4 S L51 AND (REVERSION OR REVERTANTS)
                E WHATMORE A M/AU
L55           6 S E3
L56        4081 S (SIV OR SIMIAN IMMUNODEFICIENCY VIRUS)
L57         446 S L56 AND (NEF)
L58          22 S L57 AND (REVERSION OR REVERTANTS)
                E KIRCHOFF/AU
                E KIRCHOFF F/AU
L59           1 S E3
                E KIRCHHOFF F/AU
L60          45 S E3
L61          21 S L60 AND NEF
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L1 ANSWER 1 OF 3 USPATFULL
2000:27801 Gibbon ape leukemia virus-based retroviral vectors.
Eiden, Maribeth V., Bethesda, MD, United States
Wilson, Carolyn A., Arlington, VA, United States
Deacon, Nicholas J. , Balwyn, Australia
Hooker, David J., Mill Park, Australia
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
US 6033905 20000307
WO 9423048 19941013
APPLICATION: US 1997-716351 19970224 (8)
WO 1994-US3784 19940406 19970224 PCT 371 date 19970224 PCT 102(e) date
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides replication-defective hybrid retroviral vectors comprising GaLV components and methods for preparing and using such vectors. The vectors comprise a envelope component, a core component and a defective genome, at least one of which is derived from GaLV. The vectors can comprise the minimal cis acting sequences from GaLV that allow packaging of the defective genome in a hybrid virion.

L1 ANSWER 2 OF 3 USPATFULL
2000:7162 Methods for the detection of non-pathogenic HIV-1 strains containing deletions in the Nef coding region and U3 region of the LTR.
Deacon, Nicholas John , Balwyn, Australia
McPhee, Dale Alan, Fitzroy, Australia
Crowe, Suzanne, South Yarra, Australia
The Macfarlane Burnet Centre for Medical Research Limited, Fairfield, Australia (non-U.S. corporation)
US 6015661 20000118
APPLICATION: US 1995-488551 19950607 (8)
PRIORITY: AU 1995-3021 19950517
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed toward immunologic- and nucleic acid-based methodologies for the detection of non-pathogenic human immunodeficiency virus type 1 (HIV-1) strains in the body fluids of HIV-infected individuals. A blood donor infected with HIV-1 and a cohort of six blood or blood product recipients infected from this donor were studied. These patients, who remained free of HIV-1-related disease and displayed stable and normal CD4 lymphocyte counts 10 to 14 years after infection, were termed long-term nonprogressors (LTNPs). The molecular characterization of HIV-1 sequences obtained from either virus isolates or patient peripheral blood mononuclear cells (PBMCs) of LTNPs identified similar deletions in the nef gene and in the region of overlap of nef and the U3 region of the long terminal repeat (LTR). These deletions corresponded to amino acids 166-206, or nucleotides 9281 to 9437, of the HIV-1.sub.NL43 nef/LTR region. Methods were developed to detect the presence of nonpathogenic HIV-1 strains carrying these deletions in HIV-infected patients.

CLM What is claimed is:
1. A method for detecting a non-pathogenic HIV-1 strain in the body fluids of an HIV infected individual comprising: (a) obtaining and preparing a biological sample from said HIV infected individual; (b) admixing an aliquot of said sample with an HIV-1.sub.NL43 Nef peptide consisting of amino acids 166-206; (c) admixing an aliquot of said sample with an HIV-1.sub.NL43 Nef peptide wherein said peptide contains a known HIV-1 antigenic determinant but excludes amino acids 166-206 of

Nef; (d) detecting the formation of antigen/antibody complexes of the samples of steps (a) and (b); wherein the absence of immune complex formation in step (b) and the presence of immune complex formation in step (c) is indicative of said individual being infected with a non-pathogenic HIV-1 strain.

2. A method according to claim 1 wherein the peptide of step (c) comprises amino acids 15-27 of Nef.

3. A method for detecting a non-pathogenic HIV-1 strain in the body fluids of an HIV infected individual comprising: (a) obtaining and preparing a biological sample from said HIV infected individual; (b) determining the nucleotide sequence of a portion of the nef gene and U3 region of the long terminal repeat comprising nucleotides 9281-9437; wherein the nucleotide numbering scheme employed is based upon isolate HIV-1.sub.NL43 and the presence of a deletion of nucleotides 9281-9437 in the nef gene and U3 region of the long terminal repeat is indicative of a non-pathogenic HIV-1 strain.

4. A method for detecting a non-pathogenic HIV-1 strain in the body fluids of an HIV infected individual comprising: (a) obtaining and preparing a biological sample from said HIV infected individual; (b) admixing an aliquot of said sample with an antibody specific for an epitope contained within amino acids 166-206 of an HIV-1.sub.NL43 Nef peptide; (c) admixing an aliquot of said sample with an antibody specific for an HIV-1.sub.NL43 Nef peptide, excluding amino acids 166-206; (d) detecting the formation of antigen/antibody complexes in steps (b) and (c); wherein the absence of immune complex formation in step (b) and the presence of immune complex formation in step (c) is indicative of said individual being infected with a non-pathogenic HIV-1 strain.

5. A method according to claim 4 wherein the antibody of step (c) is specific for an epitope contained within amino acids 15-27 of said Nef peptide.

L1 ANSWER 3 OF 3 USPATFULL
2000:1738 Non-pathogenic strains of HIV-1 containing mutations in the NEF gene or the U3 region of the long terminal repeat.
Deacon, Nicholas John , Balwyn, Australia
Learmont, Jennifer Catherine, Patongo, Australia
McPhee, Dale Alan, Fitzroy, Australia
Crowe, Suzanne, South Yarra, Australia
Cooper, David, Bellevue Hill, Australia
Macfarlane Burnet Centre for Medical Research Limited, Victoria, Australia (non-U.S. corporation)Australian Red Cross Society, Sidney, Australia (non-U.S. corporation)
US 6010895 20000104
APPLICATION: US 1995-388353 19950214 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention is directed toward non-pathogenic human immunodeficiency virus type 1 (HIV-1) strains containing deletions in the nef gene and U3 region of the long terminal repeat (LTR). A blood donor infected with HIV-1 and a cohort of six blood or blood product recipients infected from this donor were identified. These individuals, who remained free of HIV-1-related disease with stable and normal CD4.sup.+ lymphocyte counts 10 to 14 years after infection, were termed long-term nonprogressors (LTNPs). The molecular characterization of HIV-1

sequences obtained from either virus isolates or patient peripheral blood mononuclear cells (PBMCs) of LTNPs identified similar deletions in the nef gene and in the region of overlap of nef and the U3 region of the LTR. Full-length sequencing of one isolate genome and amplification of selected HIV-1 genome regions from other cohort members revealed no other abnormalities of obvious functional significance. These deletions corresponded to amino acids 166-206, or nucleotides 9281 to 9437, of the HIV-1.sub.NL43 nef/LTR region. These data illustrate the importance of nef or the U3 region of the LTR in determining the pathogenicity of HIV-1. These non-pathogenic strains should prove useful, inter alia, in the development of HIV-1-specific diagnostic reagents.

CLM What is claimed is:

1. An isolated non-pathogenic HIV-1 strain comprising a genomic deletion in the region corresponding to nucleotides 9281-9438 of the nef gene and U3 long terminal repeat, wherein said nucleotide numbering is based upon HIV-1 strain NL4-3 and said deletion corresponds to amino acids 166-206 of the nef protein.

2. The HIV-1 strain of claim 1 wherein said deletion results in reduced expression of the nef gene product.

3. The HIV-1 strain of claim 1 wherein said deletion results in the expression of a truncated nef gene product.

4. The HIV-1 strain of claim 1 wherein said strain is recognized by HIV-1, gp41-45-, gp120-and/or gp160-specific antibodies and is capable of stimulating an immune response in humans to at least one of the gag, pol, or env gene products without reducing proliferative responses and cytokine production to a mitogen.

5. An isolated non-pathogenic HIV-1 strain comprising a genomic deletion of at least 10 nucleotides in the region corresponding to nucleotides 9281-9438 of the nef gene and U3 long terminal repeat, wherein said nucleotide numbering is based upon HIV-1 strain NL4-3.

6. An HIV-1 strain selected from the group of viruses having the ECACC designations V94101706, V941031169, and V95031022.

7. An immunogenic composition comprising the HIV-1 strain of claim 1.

L3 ANSWER 3 OF 3 USPATFULL
1999:121536 Therapeutic compounds.
Azad, Ahmed Abdullah, Melbourne, Australia
Curtain, Cyril C, Melbourne, Australia
Greenway, Alison Louise, Melbourne, Australia
McPhee, Dale Alan , Melbourne, Australia
MacReadie, Ian, Melbourne, Australia
Biomolecular Research Institute Ltd., Parkville, Australia (non-U.S. corporation)MacFarlane Burnet Centre For Medical Research Ltd.- Fairfield Hospital, Fairfield, Australia (non-U.S. corporation)Commonwealth Scientific and Industrial Research Organisation, Parkville, Australia (non-U.S. corporation)
US 5962635 19991005
WO 9426776 19941124
APPLICATION: US 1996-553271 19960306 (8)
WO 1994-AU254 19940518 19960306 PCT 371 date 19960306 PCT 102(e) date
PRIORITY: AU 1993-8861 19930518
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A biologically-active peptide fragment of the Nef protein of human immunodeficiency virus is provided, pharmaceutical compositions comprising the peptide, analogs or derivatives of the peptide and therepeutic and screening methods which utilize the peptide and compositions which comprise them. The invention is particularly useful in the suppression of the immnune respons or in the suppression of symptoms of autoimmune disease.

CLM What is claimed is:

1. A substantially pure immunosuppressive peptide, said peptide corresponding to amino acids 2-19 of the N-terminal sequence of Nef, or an immunosuppressive analogue or derivative thereof.

2. The immunosuppressive peptide according to claim 1, wherein said peptide perturbs the membrane of immune cells.

3. The immunosuppressive peptide according to claim 1, wherein said peptide downregulates expression of CD4.

4. The immunosuppressive peptide according to claim 1, wherein said peptide binds to cellular signal transduction proteins.

5. The peptide according to claim 3, wherein said Nef.sub.2-19 peptide is linked to an Nef sequence which is optionally adjacent to Nef.sub.2-19.

6. A substantially pure immunosuppressive peptide, said peptide corresponding to amino acids 2-22 of the N-terminal sequence of Nef, or an immunosuppressive analogue or derivative thereof.

7. The immunosuppressive peptide according to claim 6, wherein said peptide perturbs the membrane of immune cells.

8. The immunosuppressive peptide according to claim 6, wherein said peptide downregulates expression of CD4.

9. The immunosuppressive peptide according to claim 6, wherein said peptide binds to cellular signal transduction proteins.

10. The peptide according to claim 8, wherein said Nef.sub.2-22 is linked to an Nef sequence which is optionally adjacent to Nef.sub.2-22.

11. A method of suppression of an immune response or of symptoms of autoimmune disease, comprising the step of administering to a subject in need of such treatment an effective amount of a peptide according to claim 1.

12. The method according to claim 11 wherein the N-terminal sequence of said peptide comprises an immunosuppressive region of Nef.sub.2-19.

13. The method according to claim 11, wherein said Nef.sub.2-19 peptide is linked to an Nef sequence which is optionally adjacent to Nef.sub.2-19.

14. A method of suppression of an immune response or of symptoms of autoimmune disease, comprising the step of administering to a subject in need of such treatment an effective amount of a peptide according to claim 6.

15. The method according to claim 14 wherein the N-terminal sequence of said peptide comprises an immunosuppressive region of Nef.sub.2-19.

16. The method according to claim 14, wherein said Nef.sub.2-22 peptide is linked to an Nef sequence which is optionally adjacent to Nef.sub.2-22.

17. A pharmaceutical composition comprising as active component an immunosuppressive analogue according to claim 1, together with a pharmaceutically-acceptable carrier.

18. The composition according to claim 17, wherein said Nef.sub.2-19 peptide is linked to an Nef sequence which is optionally adjacent to Nef.sub.2-19.

19. A pharmaceutical composition comprising as active component an immunosuppressive analogue according to claim 6, together with a pharmaceutically-acceptable carrier.

20. The composition according to claim 19, wherein said Nef.sub.2-22 peptide is linked to an Nef sequence which is optionally adjacent to Nef.sub.2-22.

L10 ANSWER 2 OF 73 USPATFULL
2000:146160 Defective viral ***vaccine*** particles obtained in vivo or ex vivo.
Klatzmann, David, Paris, France
Salzmann, Jean-Loup, Paris, France
Universite Pierre et Marie Curie (Paris VI), Paris, France (non-U.S. corporation)
US 6140114 20001031
APPLICATION: US 1998-166147 19981005 (9)
DOCUMENT TYPE: Utility.

AB The present invention relates to a ***vaccine*** consisting of defective viral particles as are obtained in vivo or ex vivo, in individuals infected or capable of being infected with a virus, after expression of the genes carried by a vector or a combination of vectors and comprising at least the structural genes necessary for the constitution of the viral particle.

L10 ANSWER 3 OF 73 USPATFULL
2000:145889 Peptide compositions for the treatment of ***HIV*** .
Rubinstein, Arye, Monsey-Wesley Hills, NY, United States
Bloom, Barry R., Hastings on Hudson, NY, United States
Devash, Yair, Princeton Junction, NJ, United States
Cryz, Stanley J., Berne, Switzerland
Albert Einstein College of Medicine of Yeshiva University, Bronx, NY, United States (U.S. corporation)
US 6139843 20001031
APPLICATION: US 1997-946525 19971007 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides for peptide conjugate compositions, methods of using the peptide conjugate compositions, and pharmaceutical compositions comprising the peptide conjugate compositions. The peptide conjugate compositions comprise peptides with amino acid sequences similar to the gp120 principal neutralizing domain (PND) of ***HIV*** , gp41, and ***Nef*** (p27) of ***HIV*** and carriers which enhance immunogenicity. The peptide conjugate compositions of the present invention may comprise a multivalent cocktail of several different peptide conjugates. Also provided by present invention is a

method for reducing the level of ***HIV*** titers in a mammal by administering to the mammal a peptide composition of the present invention in an amount effective to reduce the level of ***HIV*** titers. The peptide conjugate compositions of the present invention induce prolonged antibody response in serum, a high level of antibody in the mucosa, and the production of cytotoxic lymphocytes. The peptide conjugate compositions of the present invention also elicit neutralizing antibodies and decrease viral loads in a subject.

L10 ANSWER 9 OF 73 USPATFULL
2000:27798 Vector comprising a replication competent ***HIV*** -1 provirus and a heterologous gene.
Haseltine, William A., Cambridge, MA, United States
Terwilliger, Ernest, Boston, MA, United States
Dana-Farber Cancer Institute, Boston, MA, United States (U.S. corporation)
US 6033902 20000307
APPLICATION: US 1992-987572 19921208 (7)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A vector comprising an ***HIV*** segment and a heterologous gene segment, which produces a replication competent and an infective ***HIV*** virus is disclosed. When the heterologous gene is a marker gene, the spread of the virus can be observed in both in vitro and in vivo systems. The use of this vector in establishing methods for screening anti-viral compounds is also disclosed.

CLM What is claimed is:
1. A vector comprising: (a) a sufficient number of nucleotides corresponding to an ***HIV*** genome to express ***HIV*** gene products necessary for viral replication and infectivity (the ***HIV*** segment); and inserted in the ***HIV*** segment (i) in a region of non-essential ***HIV*** nucleotide sequences or (ii) instead of a region of non-essential ***HIV*** nucleotide sequences (b) a sufficient number of nucleotides corresponding to a heterologous gene to express a functional protein (the heterologous gene segment).

2. The vector of claim 1, wherein the heterologous gene segment corresponds to a marker gene.

3. The method of claim 2, wherein the ***HIV*** segment corresponds to nucleotides of the ***HIV*** -1 or ***HIV*** -2 genomes.

4. The vector of claim 3, wherein the ***HIV*** segment corresponds to nucleotides of the ***HIV*** -1 genome.

5. The vector of claim 2, wherein the marker gene is a chloramphenicol acetyltransferase gene or a growth hormone gene.

6. The vector of claim 2, wherein the size of the total vector is less than about 900 nucleotide bases greater than the size of the ***HIV*** -1 or ***HIV*** -2 genome.

7. The vector of claim 2, wherein the total size of the vector is no more than about 520 nucleotide bases longer than the ***HIV*** genome.

8. The vector of claim 2, wherein the vector is no more than about 700 nucleotide bases longer than the ***HIV*** -1 or ***HIV*** -2 genome.

9. The vector of claim 2, wherein the heterologous gene segment is inserted in the ***HIV*** segment instead of the region of non-essential ***HIV*** nucleotide sequences wherein the non-essential nucleotide sequences are in the 3' end of the ***HIV*** genome.

10. The vector of claim 2, wherein the heterologous gene segment is inserted in the ***HIV*** segment instead of the region of non-essential ***HIV*** nucleotide sequences wherein the non-essential nucleotides are in the 3' ***nef*** sequence of the ***HIV*** genome.

11. The vector of claim 4, heterologous gene segment is inserted in the ***HIV*** segment instead of the region of non-essential ***HIV*** nucleotide sequences region of the ***HIV*** genome wherein the non-essential ***HIV*** nucleotide sequences correspond to the 51 3' nucleotides in the env gene, the intervening nucleotides in the 3' direction until a KpnI site located 60 nucleotides 5' to the beginning of the 3' LTR.

L10 ANSWER 11 OF 73 USPATFULL
2000:7162 Methods for the detection of ***non*** - ***pathogenic*** ***HIV*** -1 strains containing deletions in the ***Nef*** coding region and U3 region of the LTR.
Deacon, Nicholas John, Balwyn, Australia
McPhee, Dale Alan, Fitzroy, Australia
Crowe, Suzanne, South Yarra, Australia
The Macfarlane Burnet Centre for Medical Research Limited, Fairfield, Australia (non-U.S. corporation)
US 6015661 20000118
APPLICATION: US 1995-488551 19950607 (8)
PRIORITY: AU 1995-3021 19950517
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed toward immunologic- and nucleic acid-based methodologies for the detection of ***non*** - ***pathogenic*** ***human*** ***immunodeficiency*** ***virus*** type 1 (***HIV*** -1) strains in the body fluids of ***HIV*** -infected individuals. A blood donor infected with ***HIV*** -1 and a cohort of six blood or blood product recipients infected from this donor were studied. These patients, who remained free of ***HIV*** -1-related disease and displayed stable and normal CD4 lymphocyte counts 10 to 14 years after infection, were termed long-term nonprogressors (LTNPs). The molecular characterization of ***HIV*** -1 sequences obtained from either virus isolates or patient peripheral blood mononuclear cells (PBMCs) of LTNPs identified similar deletions in the ***nef*** gene and in the region of overlap of ***nef*** and the U3 region of the long terminal repeat (LTR). These deletions corresponded to amino acids 166-206, or nucleotides 9281 to 9437, of the ***HIV*** -1.sub.NL43 ***nef*** /LTR region. Methods were developed to detect the presence of nonpathogenic ***HIV*** -1 strains carrying these deletions in ***HIV*** -infected patients.

L10 ANSWER 12 OF 73 USPATFULL
2000:1738 ***Non*** - ***pathogenic*** strains of ***HIV*** -1 containing mutations in the ***NEF*** gene or the U3 region of the long terminal repeat.
Deacon, Nicholas John, Balwyn, Australia
Learmont, Jennifer Catherine, Patongo, Australia
McPhee, Dale Alan, Fitzroy, Australia

Crowe, Suzanne, South Yarra, Australia
Cooper, David, Bellevue Hill, Australia
Macfarlane Burnet Centre for Medical Research Limited, Victoria, Australia (non-U.S. corporation)Australian Red Cross Society, Sidney, Australia (non-U.S. corporation)
US 6010895 20000104
APPLICATION: US 1995-388353 19950214 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention is directed toward ***non*** - ***pathogenic*** ***human*** ***immunodeficiency*** ***virus*** type 1 (***HIV*** -1) strains containing deletions in the ***nef*** gene and U3 region of the long terminal repeat (LTR). A blood donor infected with ***HIV*** -1 and a cohort of six blood or blood product recipients infected from this donor were identified. These individuals, who remained free of ***HIV*** -1-related disease with stable and normal CD4.sup.+ lymphocyte counts 10 to 14 years after infection, were termed long-term nonprogressors (LTNPs). The molecular characterization of ***HIV*** -1 sequences obtained from either virus isolates or patient peripheral blood mononuclear cells (PBMCs) of LTNPs identified similar deletions in the ***nef*** gene and in the region of overlap of ***nef*** and the U3 region of the LTR. Full-length sequencing of one isolate genome and amplification of selected ***HIV*** -1 genome regions from other cohort members revealed no other abnormalities of obvious functional significance. These deletions corresponded to amino acids 166-206, or nucleotides 9281 to 9437, of the ***HIV*** -1.sub.NL43 ***nef*** /LTR region. These data illustrate the importance of ***nef*** or the U3 region of the LTR in determining the pathogenicity of ***HIV*** -1. These ***non*** - ***pathogenic*** strains should prove useful, inter alia, in the development of ***HIV*** -1-specific diagnostic reagents.

L10 ANSWER 13 OF 73 USPATFULL
1999:155520 Method and means for producing high titer, safe, recombinant lentivirus vectors.
Naldini, Luigi, San Carlos, CA, United States
Dull, Thomas, San Francisco, CA, United States
Farson, Deborah A., Oakland, CA, United States
Witt, Rochelle, San Francisco, CA, United States
Cell Genesys, Inc., Foster City, CA, United States (U.S. corporation)
US 5994136 19991130
APPLICATION: US 1997-989394 19971212 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Lentiviral vectors modified at the 5' LTR or both the 5' and 3' LTR's are useful in the production of recombinant lentivirus vectors. Such vectors can be produced in the absence of a functional tat gene. Multiple transformation of the host cell with the vector carrying the transgene enhances virus production.

L10 ANSWER 15 OF 73 USPATFULL
1999:146625 Method for inhibiting intracellular viral replication.
Leung, David W., Mercer Island, WA, United States
Underiner, Gail E., Malvern, PA, United States
Singer, Jack W., Seattle, WA, United States
Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)
US 5985926 19991116
APPLICATION: US 1997-797326 19970210 (8)
DOCUMENT TYPE: Utility.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There is disclosed a method of preventing or delaying the occurrence of acquired immunodeficiency syndrome (AIDS) in ***human*** ***immunodeficiency*** ***virus*** (***HIV***) seropositive humans by administering an effective amount of a compound that inhibits cellular signaling through a specific phospholipid-based cellular signaling and signal amplification pathway. The invention further provides a method for preventing or delaying clinical symptoms of a group of viral diseases wherein the viral disease is mediated by host cell viral replication. The invention provides an advantage by attacking host cellular signaling mechanisms to prevent the development of drug resistance from rapidly mutating viruses.

L10 ANSWER 16 OF 73 USPATFULL
1999:146341 Non-infectious, replication-impaired, immunogenic ***human*** ***immunodeficiency*** ***virus*** type 1 retrovirus-like particles with multiple genetic deficiencies.
Haynes, Joel, Newmarket, Canada
Klein, Michel Henri, Willowdale, Canada
Rovinski, Benjamin, Thornhill, Canada
Cao, Shi Xian, Etobicoke, Canada
Connaught Laboratories Limited, North York, Canada (non-U.S. corporation)
US 5985641 19991116
APPLICATION: US 1995-467975 19950606 (8)
PRIORITY: GB 1989-12123 19891013
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An immunogenic retrovirus-like particle which is non-infectious and non-replicating and which is useful as a candidate ***vaccine*** component against retroviral infections, including AIDS and ATLL, is produced by genetic engineering. A DNA molecule comprising a retroviral genome devoid of long terminal repeats is incorporated into an expression vector, which is introduced into mammalian cells for expression of the retrovirus-like particle.

L10 ANSWER 18 OF 73 USPATFULL
1999:141683 Vectors containing ***HIV*** packaging sequences, packaging defective ***HIV*** vectors, and uses thereof.
Sodroski, Joseph G., Medford, MA, United States
Haseltine, William A., Cambridge, MA, United States
Poznansky, Mark, Cambridge, MA, United States
Lever, Andrew, Pinner, United Kingdom
Dana-Farber Cancer Institute, Boston, MA, United States (U.S. corporation)
US 5981276 19991109
APPLICATION: US 1997-915429 19970820 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Packaging defective and packaging proficient ***HIV*** vectors are disclosed. These vectors can be used to establish ***HIV*** packaging defective cell lines, and to package desired genes. These cell lines can be used in developing a ***vaccine*** , ***HIV*** antibodies and as part of a system for gene transfer. The packaging proficient vector can be used to target ***HIV*** target cells.

L10 ANSWER 19 OF 73 USPATFULL
1999:132486 Nucleic acid constructs containing ***HIV*** genes with mutated inhibitory/instability regions and methods of using same.
Pavlakis, George N., Rockville, MD, United States

Felber, Barbara K., Rockville, MD, United States
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
US 5972596 19991026
APPLICATION: US 1994-50478 19940126 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of locating an inhibitory/instability sequence or sequences within the coding region of an mRNA and modifying the gene encoding that mRNA to remove these inhibitory/instability sequences by making clustered nucleotide substitutions without altering the coding capacity of the gene is disclosed. Constructs containing these mutated genes and host cells containing these constructs are also disclosed. The method and constructs are exemplified by the mutation of a ***Human*** ***Immunodeficiency*** ***Virus*** -1 Rev-dependent gag gene to a Rev-independent gag gene. Constructs useful in locating inhibitory/instability sequences within either the coding region or the 3' untranslated region of an mRNA are also disclosed. The exemplified constructs of the invention may also be useful in ***HIV*** -1 immunotherapy and immunoprophylaxis.

L10 ANSWER 28 OF 73 USPATFULL
1999:33984 Isolation of novel ***HIV*** -2 proviruses.
Kraus, Gunter, La Jolla, CA, United States
Wong-Staal, Flossie, San Diego, CA, United States
Talbott, Randy, Princeton, NJ, United States
Poeschla, Eric M., San Diego, CA, United States
The Regents of the University of California, Oakland, CA, United States (U.S. corporation)
US 5883081 19990316
APPLICATION: US 1996-659251 19960607 (8)
PRIORITY: US 1995-1441 19950726 (60)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel ***HIV*** -2 proviruses, molecular clones, nucleic acids, polypeptides, viruses and viral components are described. The use of these compositions as components of diagnostic assays, as immunological reagents, as vaccines, as components of packaging cells, cell transduction vectors, and as gene therapy vectors is also described.

L10 ANSWER 34 OF 73 USPATFULL
1999:7231 ***Vaccine*** for protection against ***HIV*** infections, process for preparing same and their use as diagnostic and agent immunotherapeutic agent.
Dietrich, Ursula, Eschborn, Germany, Federal Republic of
Adamski, Michalina, Frankfurt, Germany, Federal Republic of
Von Briesen, Hagen, Kronberg, Germany, Federal Republic of
Kuhnel, Herbert, Egelsbach, Germany, Federal Republic of
Rubsamen-Waigmann, Helga, Bad Soden, Germany, Federal Republic of
Chemotherapeutisches Forschunginstitut Georg Speyer-Haus Zu Frankfurt A.M., Frankfurt a.M., Germany, Federal Republic of (non-U.S. corporation)
US 5861243 19990119
APPLICATION: US 1997-968689 19971112 (8)
PRIORITY: DE 1989-3934366 19891014
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB ***Vaccine*** for protection against ***HIV*** infections, ***therapeutic*** agents for treatment subsequent to ***HIV***

infections, process for their preparation and their use; procedure for differentiation between ***HIV*** -2.sub.ALT type infections and ***HIV*** -2 infections defined by the prototype ***HIV*** -2.sub.ROD.

Subject matter of the present invention are the virus ***HIV*** -2.sub.D205 as well as ***HIV*** -2 variants distinguishing from the ***HIV*** -2 prototypes of the type ***HIV*** -2.sub.ROD in that nucleotide sequence homology is less than 77%. Further, proteins and nucleic acids of ***HIV*** -2.sub.D205 and its variants for utilization as vaccines for protection against ***HIV*** infections, for geno- or immunotherapy, for establishing an animal model, and for differential diagnostics are part of this invention. Furthermore, the processes for preparing these vaccines, immunotherapeutic and diagnostic agents as well as their use are part of this invention.

L10 ANSWER 38 OF 73 USPATFULL
1998:159746 Primate lentivirus antigenic compositions.
Desrosiers, Ronald C., Hudson, MA, United States
President and Fellows of Harvard College, Cambridge, MA, United States (U.S. corporation)
US 5851813 19981222
APPLICATION: US 1994-188583 19940127 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Molecular clones of primate lentiviruses that harbor an engineered non-revertible null mutation in the ***nef*** gene and which may further include a non-revertible null mutation in one or more non-essential genetic elements, vif, vpr, vpx, vpu, Negative Regulatory Element, nuclear factor .kappa.B-binding element, or Sp1 binding element sequences are disclosed. Intact viruses containing such mutant genomes are also disclosed. These infectious, nonpathogenic viruses are capable of eliciting a protective host immune response and, thus, are useful as a ***vaccine*** that protects against AIDS in human subjects.

CLM What is claimed is:
1. An antigenic composition comprising isolated primate lentivirus whose genome contains an engineered non-revertible null mutation in the ***nef*** gene, or an infectious DNA clone thereof, in a pharmaceutically acceptable carrier.

2. The antigenic composition of claim 1, wherein said primate lentivirus further comprises engineered non-revertible null mutations in one or more nonessential genetic elements selected from the group consisting of vif, vpr, vpx, vpu, Negative Regulatory Element, nuclear factor .kappa.B-binding element, or Sp1 binding element.

3. The antigenic composition of claim 1, wherein said primate lentivirus is infectious, replication-competent, and ***non*** - ***pathogenic*** .

4. The antigenic composition of claim 1, wherein said primate lentivirus is derived from ***human*** ***immunodeficiency*** ***virus*** .

5. The antigenic composition of claim 4, wherein said primate lentivirus is derived from ***HIV*** -1.

6. The antigenic composition of claim 1, wherein said primate lentivirus is derived from simian immunodeficiency virus.

7. The antigenic composition of claim 6, wherein said primate lentivirus is derived from SIVmac.

8. The antigenic composition of claim 7, wherein said primate lentivirus is derived from the DNA clones deposited with the ATCC and designated No. 68364 and No. 68365.

9. The antigenic composition of claim 1, wherein said primate lentivirus genome further comprises an engineered non-revertible null mutation in the Negative Regulatory Element sequence.

10. The antigenic composition of claim 9, wherein said primate lentivirus genome further comprises an engineered non-revertible null mutation in the vpu or vpx gene sequence.

11. The antigenic composition of claim 1, wherein said primate lentivirus genome further comprises an engineered non-revertible null mutation in the vpr gene sequence.

12. The antigenic composition of claim 11, wherein said primate lentivirus genome further comprises an engineered non-revertible null mutation in the vpu or vpx gene sequence.

13. The antigenic composition of claim 1, wherein said primate lentivirus genome further comprises an engineered non-revertible null mutation in the vpx gene sequence.

14. The antigenic composition of claim 1, wherein said primate lentivirus genome further comprises an engineered non-revertible null mutation in the vpu gene sequence.

15. The antigenic composition of claim 7, wherein said primate lentivirus is derived from SIVmac239.DELTA. ***nef*** .DELTA.Negative Regulatory Element.

16. The antigenic composition of claim 15, wherein said primate lentivirus further comprises an engineered non-revertible null mutation in the vpx gene sequence.

17. The antigenic composition of claim 7, wherein said primate lentivirus is derived from SIVmac239.DELTA.vpr.DELTA. ***nef*** .

18. The antigenic composition of claim 17, wherein said primate lentivirus further comprises an engineered non-revertible null mutation in the vpx gene sequence.

19. The antigenic composition of claim 7, wherein said primate lentivirus is derived from SIVmac239.DELTA.3.

20. The antigenic composition of claim 7, wherein said primate lentivirus is derived from SIVmac239.DELTA.4.

21. The antigenic composition of claim 20, wherein said primate lentivirus further comprises engineered non-revertible null mutations in one or more non-essential genetic elements selected from the group consisting of vif, vpr, vpx, vpu, Negative Regulatory Element, nuclear factor .kappa.B-binding element, or Sp1 binding element.

22. The antigenic composition of claim 5, wherein said primate lentivirus is derived from ***HIV*** -1.DELTA. ***nef***

.DELTA.Negative Regulatory Element.

23. The antigenic composition of claim 22, wherein said primate lentivirus further comprises an engineered non-revertible null mutation in the vpu gene sequence.

24. The antigenic composition of claim 5, wherein said primate lentivirus is derived from ***HIV*** -1 .DELTA.vpr.DELTA. ***nef*** .

25. The antigenic composition of claim 24, wherein said primate lentivirus further comprises an engineered non-revertible null mutation in the vpu gene sequence.

26. The antigenic composition of claim 5, wherein said primate lentivirus is derived from ***HIV*** -1.DELTA.3.

27. The antigenic composition of claim 5, wherein said primate lentivirus is derived from ***HIV*** -1.DELTA.4.

28. The antigenic composition of claim 5, wherein said primate lentivirus further comprises engineered non-revertible null mutations in one or more non-essential genetic elements selected from the group consisting of vif, vpr, vpx, vpu, Negative Regulatory Element, nuclear factor .kappa.B-binding element, or Sp1 binding element.

29. A method of producing an antigenic composition comprising: transfecting cultured primate cells with primate lentiviral nucleic acid containing an engineered non-revertible null mutation of the ***nef*** gene, isolating lentivirus whose genome contains said mutation of the ***nef*** gene, and compounding said virus into a pharmaceutically acceptable antigenic compositions.

30. The method of claim 29, wherein said lentiviral nucleic acid further comprises an engineered non-revertible null mutation in the Negative Regulatory Element sequence.

31. The method of claim 29, wherein said lentiviral nucleic acid further comprises an engineered non-revertible null mutation in the vpr gene sequence.

32. The method of claim 29, wherein said lentiviral nucleic acid further comprises an engineered non-revertible null mutation in the vpx gene sequence.

33. The method of claim 29, wherein said primate lentiviral nucleic acid further comprises an engineered non-revertible null mutation in the vpu gene sequence.

L13 ANSWER 1 OF 3 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1997-012078 [01] WPIDS
DNN N1997-010462 DNC C1997-003389
TI New non-pathogenic HIV-1 isolates contain a mutation in the nef gene - and derived mutant Nef protein, useful in vaccines and for detecting non-pathogenic HIV strains.
DC B04 D16 S03
IN ***DEACON, N J*** ; GREENWAY, A L; MCPHEE, D A; MILLS, J; CROWE, S
PA (ACTR-N) ACTRACT PTY LTD; (MACF-N) MACFARLANE BURNET SYNDICATE NO 1 PTY LTD; (MACF-N) MACFARLANE BURNET CENT MEDICAL
CYC 70
PI WO 9636699 A1 19961121 (199701)* EN 94p
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN
AU 9656400 A 19961129 (199712)
US 6015661 A 20000118 (200011)
ADT WO 9636699 A1 WO 1996-AU301 19960517; AU 9656400 A AU 1996-56400 19960517; US 6015661 A CIP of US 1995-388353 19950214, US 1995-488551 19950607
FDT AU 9656400 A Based on WO 9636699
PRAI AU 1995-3021 19950517

AB WO 9636699 A UPAB: 19970102
New isolated strain of HIV-1 is: (a) non-pathogenic in humans and (b) has a modified nef gene encoding a product that is immunologically non-interactive with antibodies (Ab) to amino acids (aa) 162-177 of Nef in wild-type HIV-1. Also included are biological sources of these strains.
USE - The new strain is useful in vaccines for prevention, or treatment, of HIV infection. The methods are used to assess the risk of a HIV-positive subject developing AIDS. Also peptides corresponding to the 162-177 region can be used as immunogens (including use in vaccines) to generate Ab at higher titre than possible with a larger Nef fragment.
2bviii/2

L13 ANSWER 2 OF 3 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1995-293115 [38] WPIDS
DNC C1995-132002
TI New non-pathogenic HIV-1 strain carrying a deletion in its nef gene or LTR region - can be used in a vaccine to inhibit/reduce productive infection in an individual by a pathogenic strain.
DC B04 D16
IN COOPER, D; CROWE, S; ***DEACON, N J*** ; LEARMONT, J C; MCPHEE, D A; LEARMONT, J
PA (AURE-N) AUSTRALIAN RED CROSS SOC NSW DIV; (MACF-N) MACFARLANE BURNET CENT MEDICAL; (AURE-N) AUSTRALIAN RED CROSS SOC
CYC 63
PI WO 9521912 A1 19950817 (199538)* EN 103p
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA UG US UZ VN
AU 9517008 A 19950829 (199548)
ZA 9501182 A 19951227 (199605) 299p
EP 754223 A1 19970122 (199709) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
JP 10500281 W 19980113 (199812) 311p
EP 754223 A4 19970917 (199815)
AU 699175 B 19981126 (199908)

US 6010895 A 20000104 (200008)#
ADT WO 9521912 A1 WO 1995-AU63 19950214; AU 9517008 A AU 1995-17008 19950214; ZA 9501182 A ZA 1995-1182 19950214; EP 754223 A1 EP 1995-908826 19950214, WO 1995-AU63 19950214; JP 10500281 W JP 1995-520856 19950214, WO 1995-AU63 19950214; EP 754223 A4 EP 1995-908826 19950214; AU 699175 B AU 1995-17008 19950214; US 6010895 A US 1995-388353 19950214
FDT AU 9517008 A Based on WO 9521912; EP 754223 A1 Based on WO 9521912; JP 10500281 W Based on WO 9521912; AU 699175 B Previous Publ. AU 9517008, Based on WO 9521912
PRAI AU 1994-284 19941223; AU 1994-3864 19940214; AU 1994-4002 19940221; US 1995-388353 19950214

AB WO 9521912 A UPAB: 19950927
An isolated HIV-1 (human immunodeficiency virus type 1) strain which is substantially non-pathogenic, is new.
USE - The non-pathogenic strain of HIV-1 can be administered to infect target cells to generate target cells carrying DNA derived from them to inhibit/reduce productive infection of an individual by a pathogenic strain (claimed). This vaccination is used esp. against development of AIDS or AIDS-related diseases. The methods allow for screening/identifying cpds. which interfere with HIV-1 replication, pref. by inhibition of nef gene product function. The cpds. may be antisense or ribozyme nucleotide sequences (claimed). The pathogenicity of HIV-1 strains after infecting cells of an individual can also be determined (claimed).
Dwg.0/11

L23 ANSWER 1 OF 7 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 2000-224340 [19] WPIDS
DNC C2000-068509
TI New recombinant retrovirus for treating or preventing retroviral infection including ***human*** ***immunodeficiency*** ***virus*** (***HIV***)-1, has a modified or replaced virus envelope glycoprotein natural signal sequence.
DC B04 D16
IN KANG, C; LI, Y
PA (UYWO-N) UNIV WESTERN ONTARIO
CYC 88
PI WO 2000009703 A1 20000224 (200019)* EN 26p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9952740 A 20000306 (200030)
ADT WO 2000009703 A1 WO 1999-CA746 19990812; AU 9952740 A AU 1999-52740 19990812
FDT AU 9952740 A Based on WO 200009703
PRAI US 1998-96235 19980812

AB WO 200009703 A UPAB: 20000419
NOVELTY - A non-cytolytic recombinant virus where the natural signal sequence (NSS) of the virus envelope glycoprotein is replaced with an essentially non-cytolytic signal sequence, or is modified to provide an essentially non-cytolytic sequence, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a non-cytolytic recombinant retrovirus where the NSS of the virus' envelope glycoprotein is modified to provide an essentially non-cytolytic signal sequence;

(2) a ***vaccine*** incorporating the novel retrovirus or the retrovirus of (1);

(3) a method of preventing or treating a retroviral infection, comprising administering an essentially non-cytolytic recombinant retrovirus, where the NSS of the virus' envelope glycoprotein is replaced with an essentially non-cytolytic NSS and the retrovirus is rendered ***avirulent*** ;

(4) a method of preventing or treating a retroviral infection comprising administering to an animal, an essentially non-cytolytic recombinant retrovirus where the NSS of the virus envelope glycoprotein is modified to provide a non-cytolytic NSS;

(5) a ***vaccine*** comprising an essentially non-cytolytic recombinant retrovirus where the NSS of the virus' envelope glycoprotein is replaced with an essentially non-cytolytic NSS;

(6) a ***vaccine*** comprising an essentially non-cytolytic recombinant retrovirus where the NSS of the retrovirus envelope glycoprotein is modified to provide an essentially non-cytolytic NSS and the retrovirus is rendered ***avirulent*** ;

(7) a method of killing a target cell, comprising administering a recombinant virus containing NSS and a recognition site specific to the cell; and

(8) a method of inhibiting the effects of the NSS of a retrovirus, comprising administering an antisense oligonucleotide that is complementary to a nucleic acid sequence for an NSS protein gene to an animal

ACTIVITY - Virucide.

MECHANISM OF ACTION - ***Vaccine*** .

USE - The recombinant virus is used as a ***vaccine*** to prevent or treat a retroviral infection, especially a ***HIV*** infection (claimed).

ADVANTAGE - Unlike prior art, where avirulence has resulted in low replication, the invention provides a ***vaccine*** that is both ***avirulent*** and capable of being produced in large quantities.

Dwg.2/12

L23 ANSWER 2 OF 7 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 2000-116336 [10] WPIDS
DNC C2000-035485
TI Novel post-transcriptional regulatory elements used to construct ***attenuated*** retroviruses for vaccines.
DC B04 D16
IN NAPPI, F; PAVLAKIS, G N
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 86
PI WO 9961596 A2 19991202 (200010)* EN 59p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9940882 A 19991213 (200020)
ADT WO 9961596 A2 WO 1999-US11082 19990518; AU 9940882 A AU 1999-40882 19990518
FDT AU 9940882 A Based on WO 9961596
PRAI US 1998-86487 19980522

AB WO 9961596 A UPAB: 20000228
NOVELTY - A novel post-transcriptional regulatory element (PRE) that can function as a post-transcriptional RNA nucleo-cytoplasmic transport element (NCTE) is new. The PRE is used to replace the NCTE of ***HIV***

, producing a virus with lower replicative activity, resulting in an ***attenuated*** virus.

DETAILED DESCRIPTION - An isolated nucleic acid consists of a PRE nucleic acid (I) defined as having the following properties:

(1) the PRE nucleic acid, when inserted in a recombinant, hybrid HIVG-1, is capable of functioning as a NCTE in place of wild-type NCTE in the hybrid ***HIV*** -1, and when the PRE- containing hybrid ***HIV*** -1 virus infects activated human peripheral blood mononuclear cells (huPBMCs), the level of expression of ***HIV*** -1 p24-gag is between 2 and 200 fold (especially between 10 and 50 fold) less than in wild type virus; and

(2) the PRE has at least 80 (preferably 90)% nucleic acid identity to the, or is the, 241 bp sequence given in the specification.

INDEPENDENT CLAIMS are also included for the following:

(1) an isolated transcription product of (I);

(2) n expression cassette (especially an expression vector) comprising a nucleic acid encoding (I);

(3) transfected cell comprising a nucleic acid encoding (I);

(4) recombinant retrovirus which either lacks or has non functional endogenous NCTEs, further comprising (I) operatively inserted into the retrovirus, the PRE capable of acting as an exogenous NCTE to reconstitute the lacking or non functional endogenous NCTE and to reconstitute the infectivity of the retrovirus in a mammalian cell;

(5) a ***vaccine*** for the prophylaxis or amelioration of a viral infection in a mammal, comprising an ***attenuated*** retrovirus which lacks an endogenous functional NCTE and/or the ability to express an endogenous functional NCTE binding protein and further comprising (I), and

(6) a kit for the prophylaxis or amelioration of a viral infection in a mammal, comprising the ***vaccine*** of (5) and a carrier.

USE - The nucleic acids and oligonucleotides of the invention can be delivered into cells in a culture, tissues and organisms for synthesis, mutation and screening. When the post-transcriptional regulatory element (PRE) is used to replace the post-transcriptional RNA nucleo-cytoplasmic transport element (NCTE) of viruses, especially retroviruses such as ***HIV*** , an ***attenuated*** virus is produced, which may be used in a viral ***vaccine*** for the prophylaxis or amelioration of a viral infection in a mammal.

ADVANTAGE - None given.

Dwg.0/0

L23 ANSWER 3 OF 7 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1999-527631 [44] WPIDS
DNC C1999-155100
TI New vector useful as a ***vaccine*** for DNA immunization and prevention of ***HIV*** .
DC B04 D16
IN KROHN, K; PETERSON, P; RANKI, P A; TAEHTINEN, M
PA (FIIM-N) FINNISH IMMUNOTECHNOLOGY LTD
CYC 84
PI WO 9943841 A1 19990902 (199944)* EN 36p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9926266 A 19990915 (200004)
FI 9800463 A 19990927 (200015)
FI 105105 B1 20000615 (200035)
ADT WO 9943841 A1 WO 1999-FI152 19990226; AU 9926266 A AU 1999-26266 19990226; FI 9800463 A FI 1998-463 19980227; FI 105105 B1 FI 1998-463 19980227

FDT AU 9926266 A Based on WO 9943841; FI 105105 B1 Previous Publ. FI 9800463
PRAI FI 1998-463 19980227

AB WO 9943841 A UPAB: 19991026
NOVELTY - A self-replicating recombinant vector comprising papilloma virus nucleotide sequences consisting essentially of a papilloma E1 and E2 genes, a minimal origin of replication and a minichromosomal maintenance element of a papilloma virus, and a heterologous nucleotide sequence encoding the ***HIV*** regulatory protein ***NEF*** , REV or TAT or an immunologically active fragment of.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a ***vaccine*** containing the new vetor;
(2) preparation of the vector; and
(3) a host cell comprising the vector.
ACTIVITY - Anti- ***HIV*** .
MECHANISM OF ACTION - None given.
USE - The new vector is useful as a ***vaccine*** for DNA immunization and prevention against ***HIV*** (claimed). The vector may also be used to treat ***HIV*** (claimed). Macaca fascicularis monkeys were immunized with a mixture of the new vector constructs containing ***Nef*** , Rev or Tat. 100 mu g of each vector was administered twice. 10 % of the target cell expressing corresponding ***HIV*** -1 antigen was lysed, compared to 0 % of controls.
ADVANTAGE - There is currently no ***vaccine*** for ***HIV*** or AIDS. DNA immunization is safer than ***attenuated*** viral vaccines.
Dwg.0/7

L23 ANSWER 4 OF 7 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1999-405514 [34] WPIDS
DNC C1999-119810
TI New nucleic acid containing a constitutive transport element from an intracisternal A particle.
DC B04 D16
IN FELBER, B K; TABERNERO, C; ZOLOTUKHIN, A S
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 84
PI WO 9933992 A1 19990708 (199934)* EN 64p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9920981 A 19990719 (199951)
ADT WO 9933992 A1 WO 1998-US27792 19981229; AU 9920981 A AU 1999-20981 19981229
FDT AU 9920981 A Based on WO 9933992
PRAI US 1997-70204 19971231

AB WO 9933992 A UPAB: 19990825
NOVELTY - An isolated nucleic acid (A) consisting of a constitutive transport element derived from CTE-IAP nucleotide sequence (NS), is new.
DETAILED DESCRIPTION - An isolated nucleic acid (A) consisting of a constitutive transport element derived from CTE-IAP nucleotide sequence (NS), the isolated CTEIAP nucleic acid having the following properties:
(a) the CTEIAP, when inserted in a recombinant, hybrid ***HIV*** -1, is capable of functioning as a post-transcriptional RNA nucleo-cytoplasmic transport element (NCTE) in place of wild-type NCTE in the hybrid ***HIV*** -1, and when the CTEIAP-containing hybrid

HIV -1 virus infects activated human peripheral blood mononuclear cells (hPBMCs), the level of expression of ***HIV*** -1 p24gag is 50 to 200-fold less than levels of p24gag expression when ***HIV*** -1 wild type virus, utilizing wild-type NCTE, infects activated hPBMCs; and

(b) the secondary structure of the CTEIAP comprises at least a 2 loop A domain and a loop B domain, where the nucleic acid primary sequence of the loops has at least 90% nucleic acid sequence identity, to a loop A and a loop B domain of a nucleic acid comprising a loop structure as shown in the specification and in sequence (I) given in the specification; and the distance between the loop A domain and the loop B domain is between 11 and 36 base pairs in length.

INDEPENDENT CLAIMS are also included for the following:

(1) an isolated transcription product of a CTEIAP nucleic acid, the CTEIAP having properties as in (A) (a) and (b);

(2) an expression vector comprising a nucleic acid encoding a CTEIAP nucleic acid and a non-naturally occurring nucleic acid sequence, the CTEIAP nucleic acid having properties as in (A) (a) and (b);

(3) a transfected cell comprising a polynucleotide (PN) encoding a CTEIAP nucleic acid and a non-naturally occurring nucleic acid sequence, the CTEIAP nucleic acid having properties as in (A) (a) and (b);

(4) a recombinant retrovirus which either lacks or has non-functional endogenous post-transcriptional RNA NCTEs, further comprising a CTEIAP operatively inserted into the retrovirus, the CTEIAP capable of acting as an exogenous functional NCTE to reconstitute the lacking or non-functional endogenous NCTE and to reconstitute the infectivity of the retrovirus in a mammalian cell, the CTEIAP having properties as in (A) (a) and (b);

(5) a ***vaccine*** for the prophylaxis or amelioration of a viral infection in a mammal comprising an ***attenuated*** retrovirus, where the ***attenuated*** retrovirus, when administered as a ***vaccine*** is capable of eliciting an immune response to the retrovirus in a mammal with a functional immune system, where the ***attenuated*** retrovirus lacks an endogenous functional post-transcriptional NCTE and/or the ability to express an endogenous functional NCTE binding protein, and the ***attenuated*** retrovirus further comprises a CTEIAP nucleic acid having properties as in (A) (a) and (b);

(6) a kit for the prophylaxis or amelioration of a virus infection in a mammal, the kit comprising a ***vaccine*** as in (5) and a carrier;

(7) a method for eliciting an immune response to a virus in a mammal by administering to a mammal an ***attenuated*** recombinant virus comprising CTEIAP; and

(8) a method for screening for a post-transcriptional RNA NCTE binding protein comprising:

(a) providing a composition comprising a loop A and/or a loop B of a CTEIAP;

(b) contacting the composition with a test compound; and

(c) measuring the ability of the test compound to bind the NCTE.

ACTIVITY - Antiviral.

MECHANISM OF ACTION - The CTEIAP, when inserted in a recombinant, hybrid ***HIV*** -1, is capable of functioning as a post-transcriptional RNA NCTE in place of wild-type NCTE in the hybrid ***HIV*** -1, and when the CTEIAP-containing hybrid ***HIV*** -1 virus infects activated hPBMCs, the level of expression of ***HIV*** -1 p24gag is 50 to 200-fold less than levels of p24gag expression when ***HIV*** -1 wild type virus, utilizing wild-type NCTE, infects activated hPBMCs.

USE - The CTEIAP can be used to produce ***attenuated*** retroviruses. The product can be used for the prophylaxis or amelioration of a viral infection, particularly ***HIV*** -1 infection (claimed).

Dwg.0/4

L23 ANSWER 5 OF 7 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1999-024005 [02] WPIDS
DNN N1999-018490 DNC C1999-007264
TI Use of immunodeficient mice comprising human cells - particularly SCTD/beige mice comprising human immune cells for evaluating vaccines against cancers or human pathogens, e.g. ***HIV*** .
DC B04 D16 P14
IN CHANG, L
PA (CHAN-I) CHANG L
CYC 74
PI WO 9844788 A2 19981015 (199902)* EN 155p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AU BA BB BG BR CA CN CU CZ EE GE GW HU ID IL IS JP KP KR LC LK LR LT LV MG MK MN MX NO NZ PL RO SG SI SK SL TR TT UA US UZ VN YU ZW
AU 9868909 A 19981030 (199911)
EP 973381 A2 20000126 (200010) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9844788 A2 WO 1998-US6944 19980409; AU 9868909 A AU 1998-68909 19980409; EP 973381 A2 EP 1998-914591 19980409, WO 1998-US6944 19980409
FDT AU 9868909 A Based on WO 9844788; EP 973381 A2 Based on WO 9844788
PRAI US 1997-69163 19971209; US 1997-838702 19970409; US 1997-848760 19970501

AB WO 9844788 A UPAB: 19990113
A method is claimed comprising: (a) providing: (I) an immunodeficient mouse comprising human cells; (ii) an injectable preparation comprising at least 1 component derived from a human pathogen; and (iii) a composition comprising an infectious human pathogen; (b) injecting the mouse with the injectable preparation; (c) exposing the injected mouse to the composition; and (d) monitoring the exposed mouse for the presence of infection of the human cells by the infectious human pathogen. Also claimed are: (1) a method comprising: (a) providing: (I) a SCID/beige mouse comprising human immune cells; (ii) an injectable preparation comprising one or more components derived from a ***HIV*** ; and (iii) a composition comprising non- ***attenuated*** ***HIV*** ; (b) injecting the mouse with the injectable preparation; (c) exposing the injected mouse to the composition; and (d) monitoring the exposed mouse for the presence of infection of the human immune cells by the non- ***attenuated*** ***HIV*** ; (2) an ***attenuated*** ***HIV*** where the genome of the virus comprises a mutated tat gene and a mutated ***nef*** gene; (3) a method for analysing results from an immunospot assay comprising performing an immunospot assay where a detectable signal is converted to a digital image using an analysis device; (4) a ***vaccine*** comprising a cell modified to express an antigen and an immune-modulating protein; (5) an expression vector comprising a polynucleotide sequence that encodes an antigen and at least 1 immune-modulating protein; (6) an immunodeficient mouse comprising a number of human immune cells, capable of producingt a sustained immune response in the mouse; (7) a SCID/beige mouse comprising human immune cells; (8) a method comprising: (a) providing: (I) a SCID/beige mouse; (ii) human tumour cells; and (iii) human peripheral blood lymphocytes (PBLs); (b) introducing a first dose of the tumour cells into the mouse; (c) reconstituting the mouse containing the tumour cells with the lymphocytes; and (d) monitoring the reconstituted mouse for the growth of the tumour cells; (9) a method comprising: (a) providing: (I) a SCID/beige mouse; (ii) irradiated and unirradiated human tumour cells; and (iii) human peripheral blood lymphocytes; (b) reconstituting the mouse with the lymphocytes; (c) vaccinating the mouse with the irradiated tumour cells; (d) introducing the unirradiated tumour cells into the vaccinated mouse;

and (e) monitoring the vaccinated mouse for the growth of the unirradiated tumour cells; (10) a method of treating a subject having a tumour, comprising: (a) providing an expression vector encoding an antigen and at least 1 additional immune modulator; and (b) transferring the expression vector into the tumour such that the antigen and the immune-modulator are expressed by at least a portion of the tumour.

USE - The methods can be used for producing and evaluating vaccines including cancer vaccines and vaccines directed against human pathogens, e.g. ***HIV*** , Leishmania, Mycobacterium, Listeria or Plasmodium. The combination of an immunospot assay with a computer-assisted data acquisition and processing system simplifies the experimental procedures and can be used for the clinical or experimental assessment of general and specific immune responses, especially when dealing with a large sample size.

Dwg.0/16

L23 ANSWER 6 OF 7 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1994-279391 [34] WPIDS
DNC C1994-127476
TI Multiple gene mutants of ***human*** ***immunodeficiency*** ***virus*** - provide safe ***attenuated*** ***vaccine*** for treatment and prophylaxis of ***HIV*** .
DC B04 D16
IN LOONEY, D J; WONG-STAAL, F; WONGSTAAL, F
PA (REGC) UNIV CALIFORNIA
CYC 45
PI WO 9417825 A1 19940818 (199434)* EN 28p
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE
W: AU BB BG BR BY CA CZ FI HU JP KP KR KZ LK LV MG MN MW NO NZ PL RO RU SD SK UA UZ VN
AU 9458487 A 19940829 (199501)
ADT WO 9417825 A1 WO 1993-US12088 19931213; AU 9458487 A WO 1993-US12088 19931213, AU 1994-58487 19931213
FDT AU 9458487 A Based on WO 9417825
PRAI US 1993-14318 19930205

AB WO 9417825 A UPAB: 19941013
A novel plasmid (I) comprises a proviral ***HIV*** clone and env, ***nef*** , vif and vpr regions, from which significant portions of at least three of said regions have been deleted, said plasmid exhibiting cell-free infectivity and reduced syncytium formation ability. Also claimed are: (1) prodn. of ***attenuated*** human ***HIV*** comprising: (a) providing a plasmid comprising a proviral ***HIV*** clone and env, ***nef*** , vif and vpr regions; and (b) deleting from the plasmid significant portions of at least three regions providing a plasmid exhibiting cell-free infectivity and reduced syncytium formation ability; (2) an ***attenuated*** ***HIV*** comprising (I); and (3) a ***vaccine*** for prevention or treatment of a person with ***HIV*** which comprises the ***attenuated*** ***HIV*** of (2) and a suitable carrier.

USE/ADVANTAGE - The invention provides safe immunogenic molecular clones of ***HIV*** which have been altered to exhibit minimal cytopathogenicity, impaired and/or limited infectivity and susceptibility to complete eradication by various nontoxic agents. The ***attenuated*** virus is a safe alternative to use of live virus in a ***vaccine*** , and should be safe for clinical trials.

Dwg.0/0

L23 ANSWER 7 OF 7 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1992-056816 [07] WPIDS
CR 1999-080408 [07]

DNC C1992-025655
TI Primate lentivirus ***vaccine*** protecting against AIDS - and primate lentiviruses and their DNA clones contg. null mutation(s), useful for producing ***vaccine*** .
DC B04 D16
IN DESROSIERS, R C
PA (HARD) HARVARD COLLEGE
CYC 15
PI WO 9200987 A 19920123 (199207)*
RW: AT BE CH DE DK ES FR GB GR IT LU NL SE
W: JP
EP 491930 A1 19920701 (199227) EN
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
JP 05501654 W 19930402 (199318) 16p
EP 491930 B1 19970115 (199708) EN 20p
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
DE 69124215 E 19970227 (199714)
ADT EP 491930 A1 EP 1991-913715 19910710, WO 1991-US4884 19910710; JP 05501654 W JP 1991-513074 19910710, WO 1991-US4884 19910710; EP 491930 B1 EP 1991-913715 19910710, WO 1991-US4884 19910710; DE 69124215 E DE 1991-624215 19910710, EP 1991-913715 19910710, WO 1991-US4884 19910710
FDT EP 491930 A1 Based on WO 9200987; JP 05501654 W Based on WO 9200987; EP 491930 B1 Based on WO 9200987; DE 69124215 E Based on EP 491930, Based on WO 9200987
PRAI US 1990-551945 19900712

AB WO 9200987 A UPAB: 19931006
A DNA clone (I) of a primate lentivirus, contg. an engineered non-revertible null mutation in the ref. gene, is new.

Also claimed are: (1) a primate lentivirus whose genome contains an engineered non-revertible null mutation in the ref. gene; (2) a method for producing a ***vaccine*** providing protection against a lentivirus, comprising: (a) transfecting cultured primate cells with primate lentiviral nucleic acid (NA) contg. an engineered non-revertible null mutation of the ref. gene; (b) isolating lentivirus whose genome contains the mutation; and (c) compounding the virus into a pharmaceutically acceptable ***vaccine*** ; and (3) a ***vaccine*** comprising (I) or the lentivirus of (1).

The mutation pref. leaves intact the genomic env gene sequence. (I) is derived from the genome of ***HIV*** -1 or SIVmac. It is deposited as ATCC No.68364 or 68365. It further comprises an engineered, non-revertible null mutation in the NRE sequence or vpr sequence, vpx sequence or vpu sequence.

USE - The vaccines are infectious and ***non*** - ***pathogenic*** and are capable of eliciting a protective host immune response. They are thus useful for protecting humans against AIDS.

L25 ANSWER 1 OF 22 AIDSLINE
2000:1372 Document No.: MED-20021577. Identification of a new recipient in the Sydney Blood Bank Cohort: a long-term HIV type 1-infected seroindeterminate individual. Rhodes D; Solomon A; Bolton W; Wood J; Sullivan J; Learmont J; ***Deacon N*** . AIDS Molecular Biology Unit, National Centre for HIV Virology Research, Macfarlane Burnet Centre for Medical Research, Fairfield, Victoria, Australia. AIDS RESEARCH AND HUMAN RETROVIRUSES (1999). Vol. 15, No. 16, pp. 1433-9. Journal code: ART. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB We have reported previously a cohort of long-term survivors of HIV-1 infection, known as the Sydney Blood Bank Cohort, who received HIV-1-positive blood from a common infected donor. A new recipient, C135, has been identified. This recipient became infected after receiving blood donated during the presumed time of seroconversion of the donor in February 1981. C135 has been infected for more than 18 years without signs of disease progression. The virus load in this recipient has remained below the detectable level (<20 RNA copies/ml of plasma) and repeated Western blot analyses have given an indeterminate result. By booster PCR techniques we have demonstrated that this individual is infected with HIV-1 and have characterized the viral ***nef*** and ***nef*** /LTR region sequences present. The strain of HIV-1 identified contains deletions of 88 bp from the ***nef*** alone region and a total of 139 bp deleted from the ***nef*** /LTR overlap and LTR regions. The LTR contains three wild-type Sp1 transcription factor-binding sites, the 3' wildtype NF-kappaB site, and a duplicated Sp1 and NF-kappaB region. A truncated ***Nef*** protein of only 19 amino acids is encoded. The deletions and rearrangements in the ***nef*** gene and LTR sequences are characteristic of Sydney Blood Bank Cohort strains of virus. The identification of C135 increases the Sydney Blood Bank Cohort size to nine individuals and represents a rare example of a genuine, long-term HIV-1 infection accompanied by indeterminate anti-HIV-1 serology.

L25 ANSWER 2 OF 22 AIDSLINE
1999:7933 Document No.: MED-99260703. Immunologic and virologic status after 14 to 18 years of infection with an attenuated strain of HIV-1. A report from the Sydney Blood Bank Cohort [see comments]. Learmont J C; Geczy A F; Mills J; Ashton L J; Raynes-Greenow C H; Garsia R J; Dyer W B; McIntyre L; Oelrichs R B; Rhodes D I; ***Deacon N J*** ; Sullivan J S. Australian Red Cross Blood Service-New South Wales, Sydney. jlearmont@arcbs.redcross.org.au. NEW ENGLAND JOURNAL OF MEDICINE (1999). Vol. 340, No. 22, pp. 1715-22. Journal code: NOW. ISSN: 0028-4793. Pub. country: United States. Language: English.

AB BACKGROUND AND METHODS: The Sydney Blood Bank Cohort consists of a blood donor and eight transfusion recipients who were infected before 1985 with a strain of human immunodeficiency virus type 1 (HIV-1) with a deletion in the region in which the ***nef*** gene and the long terminal repeat overlap. Two recipients have died since 1994, at 77 and 83 years of age, of causes unrelated to HIV infection; one other recipient, who had systemic lupus erythematosus, died in 1987 at 22 years of age of causes possibly related to HIV. We present longitudinal immunologic and virologic data on the six surviving members and one deceased member of this cohort through September 30, 1998. RESULTS: The five surviving recipients remain asymptomatic 14 to 18 years after HIV-1 infection without any antiretroviral therapy; however, the donor commenced therapy in February 1999. In three recipients plasma concentrations of HIV-1 RNA are undetectable (<200 copies per milliliter), and in two of these three the CD4 lymphocyte counts have declined by 9 and 30 cells per cubic millimeter per year (P=0.3 and P=0.5, respectively). The donor and two other

recipients have median plasma concentrations of HIV-1 RNA of 645 to 2850 copies per milliliter; the concentration has increased in the donor (P<0.001). The CD4 lymphocyte counts in these three cohort members have declined by 16 to 73 cells per cubic millimeter per year (P<0.001). In the recipient who died after 12 years of infection, the median plasma concentration of HIV-1 RNA was 1400 copies per milliliter, with a decline in CD4 lymphocyte counts of 17 cells per cubic millimeter per year (P=0.2). CONCLUSIONS: After prolonged infection with this attenuated strain of HIV-1, there is evidence of immunologic damage in three of the four subjects with detectable plasma HIV-1 RNA. The CD4 lymphocyte counts appear to be stable in the three subjects in whom plasma HIV-1 RNA remains undetectable.

L25 ANSWER 7 OF 22 AIDSLINE
1998:10053 Document No.: MED-98242896. Serological detection of attenuated HIV-1 variants with ***nef*** gene deletions. Greenway A L; Mills J; Rhodes D; ***Deacon N J*** ; McPhee D A. AIDS Cellular Biology Unit, National Centre in HIV Virology Research, Macfarlane Burnet Centre for Medical Research, Fairfield, Victoria, Australia. AIDS (1998). Vol. 12, No. 6, pp. 555-61. Journal code: AID. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB OBJECTIVE: To investigate whether members of a transfusion-linked cohort (the Sydney Bloodbank Cohort) infected with a ***nef*** -deleted strain of HIV-1 could be differentiated from individuals infected with wild-type strains of HIV-1 by characterizing the ***Nef*** antibody response of cohort members. DESIGN: Retrospective and prospective analysis of the ***nef*** gene sequence and the antibody response to ***Nef*** peptides in HIV-infected subjects. METHODS: Plasma was obtained from all individuals of the Sydney cohort, and from a variety of HIV-1-infected and uninfected controls. Antibodies recognizing full-length recombinant HIV-1NL43 ***Nef*** protein and synthetic peptide analogues were assessed by enzyme-linked immunosorbent assay. RESULTS: All 34 individuals infected with wild-type HIV-1 had antibodies reacting with full-length ***Nef*** protein as well as with a series of synthetic peptides (6-23-mers) spanning most of the ***Nef*** protein of HIV-1NL43. Although the HIV-1 quasispecies infecting the Sydney cohort had a consensus deletion of the ***nef*** gene corresponding to amino-acids 165-206, HIV-1 strains from individual members of the cohort had additional deletions comprising up to 80% of the ***nef*** gene. Members of the cohort had antibodies to peptides homologous to all regions of the ***Nef*** protein tested, except for a single peptide (amino-acids 162-177) that lies within the consensus ***nef*** deletion for the cohort quasispecies. CONCLUSION: These data show that ***nef*** -deleted strains of HIV-1 can be detected serologically. In the Sydney cohort, detection of antibodies to all regions of ***Nef*** tested, except that corresponding to amino-acids 162-177, suggests that observed deletions outside this domain occurred after this virus had infected these subjects and stimulated an immune response. A ***Nef*** peptide serological assay may be useful for identifying further examples of individuals infected with ***nef*** -deleted, attenuated HIV-1 quasispecies and for assessing the evolution of those variants in vivo.

L25 ANSWER 17 OF 22 AIDSLINE
1996:2979 Document No.: MED-96069819. Genomic structure of an attenuated quasi species of HIV-1 from a blood transfusion donor and recipients [see comments]. ***Deacon N J*** ; Tsykin A; Solomon A; Smith K; Ludford-Menting M; Hooker D J; McPhee D A; Greenway A L; Ellett A; Chatfield C; et al. AIDS Molecular Biology Unit, Macfarlane Burnet Centre for Medical Research, Fairfield, Victoria, Australia. SCIENCE (1995). Vol. 270, No. 5238, pp. 988-91. Journal code: UJ7. ISSN: 0036-8075. Pub.

country: United States. Language: English.

AB A blood donor infected with human immunodeficiency virus-type 1 (HIV-1) and a cohort of six blood or blood product recipients infected from this donor remain free of HIV-1-related disease with stable and normal CD4 lymphocyte counts 10 to 14 years after infection. HIV-1 sequences from either virus isolates or patient peripheral blood mononuclear cells had similar deletions in the ***nef*** gene and in the region of overlap of ***nef*** and the U3 region of the long terminal repeat (LTR). Full-length sequencing of one isolate genome and amplification of selected HIV-1 genome regions from other cohort members revealed no other abnormalities of obvious functional significance. These data show that survival after HIV infection can be determined by the HIV genome and support the importance of ***nef*** or the U3 region of the LTR in determining the pathogenicity of HIV-1.

L28 ANSWER 3 OF 43 AIDSLINE
2000:1382 Document No.: MED-20046347. Effect of long-term infection with ***nef*** -defective attenuated ***HIV*** type 1 on CD4+ and CD8+ T lymphocytes: increased CD45RO+CD4+ T lymphocytes and limited activation of CD8+ T lymphocytes. Zaunders J J; Geczy A F; Dyer W B; McIntyre L B; Cooley M A; Ashton L J; Raynes-Greenow C H; ***Learmont J*** ; Cooper D A; Sullivan J S. Centre for Immunology, St. Vincent's Hospital, Darlinghurst, NSW, Australia. j.zaunders@cfi.unsw.edu.au. AIDS RESEARCH AND HUMAN RETROVIRUSES (1999). Vol. 15, No. 17, pp. 1519-27. Journal code: ART. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Members of the Sydney Blood Bank Cohort (SBBC) have been infected with an attenuated strain of ***HIV*** -1 with a natural ***nef*** /LTR mutation and have maintained relatively stable CD4+ T lymphocyte counts for 14-18 years. Flow cytometric analysis was used to examine the phenotype of CD4+ and CD8+ T lymphocytes in these subjects, including the immunologically important naive (CD45RA+CD62L+), primed (CD45RO+), and activated (CD38+HLA-DR+ and CD28-) subsets. The median values were compared between the SBBC and control groups, comprising age-, sex-, and transfusion-matched ***HIV*** -1-uninfected subjects; transfusion-acquired ***HIV*** -1-positive LTNPs; and sexually acquired ***HIV*** -1-positive LTNPs. Members of the SBBC not only had normal levels of naive CD4+ and CD8+ T lymphocytes, but had primed CD45RO+ CD4+ T lymphocytes at or above normal levels. Furthermore, these primed cells expressed markers suggesting recent exposure to specific antigen. SBBC members exhibited variable activation of CD8+ T lymphocytes. In particular, SBBC members with undetectable plasma ***HIV*** -1 RNA had normal levels of activated CD8+ T lymphocytes. Therefore, the result of long-term infection with natural ***nef*** /LTR mutant ***HIV*** -1 in these subjects suggests a decreased cytopathic effect of attenuated ***HIV*** -1 on susceptible activated CD4+ T lymphocyte subsets in vivo, and minimal activation of CD8+ T lymphocytes.

L28 ANSWER 4 OF 43 AIDSLINE
2000:309 Document No.: MED-99429519. The Sydney Blood Bank Cohort: a case-control study using a transfused ***HIV*** -1 seronegative group. McIntyre L B; Geczy A F; Dyer W B; ***Learmont J C*** ; Sullivan J S. Australian Red Cross Blood Service-NSW, Sydney, New South Wales. ANNALS OF EPIDEMIOLOGY (1999). Vol. 9, No. 7, pp. 436-40. Journal code: BX8. ISSN: 1047-2797. Pub. country: United States. Language: English.

AB PURPOSE: To compare the immunological function of the Sydney Blood Bank Cohort (SBBC), a unique group of individuals who were all infected with a similar, attenuated strain of ***HIV*** -1, with a matched ***HIV*** -1 seronegative control group. To establish whether the asymptomatic state

of the SBBC, in 1996, was likely to continue, and whether the SBBC were free from immunological signs of disease progression. METHODS: A prospective case-control design using a matched transfused ***HIV*** -1 seronegative control group. Immunological testing was performed and compared across the groups. These measurements included CD4+, CD8+, CD3 + subsets, total lymphocytes, beta-2-microgloublin (beta2M), and neopterin. RESULTS: Significant differences were observed between the SBBC and the controls, particularly CD4% ($p < 0.05$), CD8 counts ($p < 0.01$), and CD4:CD8 ratios ($p < 0.001$). CONCLUSIONS: The results suggested that, as a group, the SBBC remained asymptomatic 12 to 16 years after infection with ***HIV*** -1. However, elevated CD8+ T lymphocytes, together with decreasing CD4%, suggested that some SBBC members were showing early immunologicalsigns of disease progression during late 1996, confirmed by recent (1998) follow-up studies.

L28 ANSWER 5 OF 43 AIDSLINE
1999:3640 Document No.: MED-99125818. Cytokine profiles in a cohort of long-term survivors of transfusion-acquired ***HIV*** -1 infection [letter]. Blasdall S A; Geczy A F; Raynes-Greenow C H; Dyer W B; McIntyre L B; ***Learmont J C*** ; Sullivan J S. JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES AND HUMAN RETROVIROLOGY (1999). Vol. 20, No. 1, pp. 97. Journal code: B7J. ISSN: 1077-9450. Pub. country: United States. Language: English.

L28 ANSWER 11 OF 43 AIDSLINE
1998:3431 Document No.: MED-98032464. Lymphoproliferative immune function in the Sydney Blood Bank Cohort, infected with natural ***nef*** /long terminal repeat mutants, and in other long-term survivors of transfusion-acquired ***HIV*** -1 infection. Dyer W B; Geczy A F; Kent S J; McIntyre L B; Blasdall S A; ***Learmont J C*** ; Sullivan J S. New South Wales Red Cross Blood Transfusion Service, Sydney, Australia. AIDS (1997). Vol. 11, No. 13, pp. 1565-74. Journal code: AID. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB OBJECTIVES: To assess T-helper cell immune function (proliferation) in members of the Sydney Blood Bank Cohort (SBBC) compared with other individuals with transfusion- and sexually acquired ***HIV*** -1 infection and with matched ***HIV*** -negative controls. DESIGN AND METHODS: Decreasing CD4 counts and T-helper cell function are associated with disease progression. Peripheral blood mononuclear cells (PBMC) from study subjects were assayed for in vitro proliferative responses to ***HIV*** -1-derived antigens, recall antigens and alloantigen. T-helper cell function and CD4 counts in members of the SBBC were followed longitudinally. RESULTS: Proliferative responses and CD4 counts from members of the SBBC were similar to or better than those of other transfusion- or sexually-acquired ***HIV*** -1-positive long-term non-progressors (LTNP), including the ***HIV*** -negative matched SBBC control groups. However, individuals with disease progression had reduced or undetectable proliferative responses to recall antigens but a conserved response to alloantigen; they also had low CD4 counts and low CD4:CD8 ratios. In the SBBC, these immune parameters were usually stable over time. CONCLUSIONS: The unique SBBC with natural ***nef*** /long terminal repeat deletions in the ***HIV*** -1 genome were genuine LTNP without showing signs of disease progression. They appeared to be a group distinct from the tail-end of the normal distribution of disease progression rates, and may remain asymptomatic indefinitely. The SBBC virus may form the basis of a live attenuated immunotherapeutic or immunoprophylactic ***HIV*** vaccine.

L28 ANSWER 36 OF 43 AIDSLINE
1994:10627 Document No.: MED-94359315. ***HIV*** infection in recipients

of blood products from donors with known duration of infection. Ashton L J; ***Learmont J*** ; Luo K; Wylie B; Stewart G; Kaldor J M. National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia. LANCET (1994). Vol. 344, No. 8924, pp. 718-20. Journal code: L0S. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.

AB From a registry of people with transfusion-acquired ***HIV*** infection, 25 recipients were identified for whom the dates of ***HIV*** infection in the 8 corresponding donors could be established. Longer times to AIDS and to death in recipients were independently associated ($p < 0.01$) with the receipt of blood from donors who developed AIDS more than 10 years after ***HIV*** infection, as well as with older age and fewer transfusions. Sex, zidovudine treatment, and severity of illness at transfusion were not significantly associated with survival.

L28 ANSWER 38 OF 43 AIDSLINE
1993:673 Document No.: MED-93023212. Long-term symptomless ***HIV*** -1 infection in recipients of blood products from a single donor [see comments]. ***Learmont J*** ; Tindall B; Evans L; Cunningham A; Cunningham P; Wells J; Penny R; Kaldor J; Cooper D A. New South Wales Red Cross Blood Transfusion Service, Sydney, Australia. LANCET (1992). Vol. 340, No. 8824, pp. 863-7. Journal code: L0S. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.

AB There have been reported cases of long-term symptomless human immunodeficiency virus type 1 (***HIV*** -1) infection, but it is not clear whether the benign course of infection was due to host, viral, or other unknown factors. During follow-up of subjects with transfusion-acquired ***HIV*** -1 infection in New South Wales, Australia, we identified a group of 6 subjects who had been infected through a single common donor. We were therefore able to study the contributions of various factors to the course of infection. Throughout follow-up (range 6.8-10.1 years after infection), 5 of the recipients and the donor (last follow-up 10.2 years after infection of the first recipient) remained clinically free of symptoms, with normal CD4 cell counts and no p24 antigenaemia. ***HIV*** -1 was isolated from only 1 recipient; the isolate did not induce syncytia in a SUPT1 co-culture assay and had a limited in-vitro host range. 1 infected recipient (who had received extensive immunosuppressive treatment for systemic lupus erythematosus) developed Pneumocystis carinii pneumonia and died 4.3 years after infection. The frequency of progression to AIDS or a CD4 cell count below 0.50 x 10(9)/l was significantly lower among the 6 subjects with a common donor (1/6) than among 101 other ***HIV*** -infected transfusion recipients for whom data from 7 years of follow-up were available (94/101; p less than 0.0001). These findings suggest that the subjects were infected by a less virulent strain of ***HIV*** -1. The identification of this group of subjects should stimulate a search for other similar groups, which will provide important information on the immunopathogenesis of ***HIV*** -1 disease.

L28 ANSWER 26 OF 43 AIDSLINE
1996:4527 Document No.: MED-96157200. A direct association between ***HIV*** and AIDS in blood transfusion donors and recipients. Sullivan J S; ***Learmont J*** ; Lumley T; Geczy A F; Cook L; Dyer W B. New South Wales Red Cross Blood Transfusion Service, Sydney, Australia. AIDS RESEARCH AND HUMAN RETROVIRUSES (1995). Vol. 11, No. 10, pp. 1147-8. Journal code: ART. ISSN: 0889-2229. Pub. country: United States. Language: English.

L28 ANSWER 27 OF 43 AIDSLINE

1996:3076 Document No.: MED-96060992. ***HIV*** and AIDS [letter; comment]. Sullivan J S; ***Learmont J C*** ; Geczy A F; Dyer W. NATURE (1995). Vol. 378, No. 6552, pp. 10. Journal code: NSC. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

L31 ANSWER 42 OF 61 AIDSLINE
1994:2458 Document No.: MED-94082455. ***Nef*** 27, but not the ***Nef*** 25 isoform of human immunodeficiency virus-type 1 pNL4.3 down-regulates surface CD4 and IL-2R expression in peripheral blood mononuclear cells and transformed T cells. Greenway A L; ***McPhee D*** *** A*** ; Grgacic E; Hewish D; Lucantoni A; Macreadie I; Azad A. National Centre in HIV Virology Research, Macfarlane Burnet Centre for Medical Research, Fairfield, Victoria, Australia. VIROLOGY (1994). Vol. 198, No. 1, pp. 245-56. Journal code: XEA. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB Continuing controversy surrounds the cellular effects of the ***Nef*** protein of ***HIV*** -1, a nonstructural protein expressed by most isolates. Highly purified protein isoforms of MW 27 kDa (***Nef*** 27) and 25 kDa (***Nef*** 25), produced in Escherichia coli by translation from the first and second start codons of ***HIV*** -1 ***nef*** clone pNL4.3, respectively, were introduced into cells by a sophisticated electroporation technique which uses electric field rather than electric charge to transfer macromolecules across cell membranes. Electroporation of ***Nef*** 27 reduced the expression of cell surface CD4 by 30-50%, as measured by flow cytometry, on phytohemagglutinin (PHA)-activated PBMC as well as on a variety of CD4+ T-cell lines (MT-2, CEM, and Jurkat). Reduction in surface CD4 was observed in all cells of the CD4+ T-cell lines but only in the CD4+ cells of the mixed PBMC population. Electroporation of ***Nef*** 27 into MT-2 cells and PHA-activated PBMC also reduced the expression of IL-2R to background levels. Other cell surface antigens analyzed such as CD2, CD7, or transferrin receptor (TfR) were not affected by the introduction of ***HIV*** -1 ***Nef*** 27. In contrast to the effects of ***Nef*** 27, electroporation of ***Nef*** 25 into cells at equivalent concentrations did not affect the surface expression of CD4 and IL-2R. These data show that the ***HIV*** -1 clone pNL4.3 ***Nef*** 27 but not the ***Nef*** 25 isoform specifically decreases expression of two cell surface receptors important for antigen recognition of MHC class II antigens and for cell proliferation. Production of ***Nef*** 27 during ***HIV*** -1 infection of cells of the immune system may contribute to immunodeficiency even in the absence of direct viral cytopathic effects.

L31 ANSWER 7 OF 61 AIDSLINE
1998:8882 Document No.: MED-98206874. Efficacy of fusion peptide homologs in blocking cell lysis and ***HIV*** -induced fusion. Silburn K A; ***McPhee D A*** ; Maerz A L; Poumbourios P; Whittaker R G; Kirkpatrick A; Reilly W G; Manthey M K; Curtain C C. AIDS Cellular Biology Unit, Macfarlane Burnet Centre for Medical Research, Fairfield, Victoria, Australia. AIDS RESEARCH AND HUMAN RETROVIRUSES (1998). Vol. 14, No. 5, pp. 385-92. Journal code: ART. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Contrary to earlier reports, we have found that tri- and hexapeptides analogous or homologous with segments of the 23-residue N-terminal fusion sequence (FS) of the viral transmembrane glycoprotein gp41 (residues 517-539) did not significantly inhibit ***HIV*** -1-induced syncytium formation, using an uninfected cell-infected cell fusion assay. In contrast, we found that the high molecular weight apolipoprotein A-1 and a 23-residue analog of the FS, with the phenylalanine residues at positions 524 and 527 replaced with alanine residues, were effective inhibitors.

Although the tripeptides were ineffective as inhibitors of syncytium formation, we found a number of them inhibited red cell lysis induced by the synthetic peptide AVGIGALFLGFLGAAGSTMGARS (based on the ***HIV*** -1 gp41 FS). This effect was also seen with apolipoprotein A-1. The Ala524,527 analog of the fusion sequence could not be tested in this system because it was hemolytic. We concluded that the smaller peptides were effective inhibitors of hemolysis because they interfered with pore formation by the fusion sequence peptide, either by disrupting the pores or by preventing the peptide from adopting the alpha-helical conformation found in the pores. On the other hand, membrane fusion, which is a prelude to syncytium formation, has been shown to require the fusion sequence in the beta-strand conformation. We argue that small peptides would be unable to block interaction between such strands, although larger molecules, such as apolipoprotein A-1 and the Ala524,527 analog, would be able to do so and thus inhibit fusion. It seems, therefore, that a successful drug directed against the FS-cell membrane interaction stage of syncytium formation would need to be of relatively high molecular weight and complexity.

L43 ANSWER 2 OF 20 AIDSLINE
2000:8978 Document No.: MED-20219431. Unusual polymorphisms in human immunodeficiency virus type 1 associated with nonprogressive infection. Alexander L; Weiskopf E; Greenough T C; Gaddis N C; Auerbach M R; Malim M H; O'Brien S J; Walker B D; Sullivan J L; ***Desrosiers R C*** . New England Regional Primate Research Center, Harvard Medical School, Southborough, Massachusetts 01772, USA. JOURNAL OF VIROLOGY (2000). Vol. 74, No. 9, pp. 4361-76. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Factors accounting for long-term nonprogression may include infection with an ***attenuated*** strain of human immunodeficiency virus type 1 (HIV-1), genetic polymorphisms in the host, and virus-specific immune responses. In this study, we examined eight individuals with nonprogressing or slowly progressing HIV-1 infection, none of whom were homozygous for host-specific polymorphisms (CCR5-Delta32, CCR2-64I, and SDF-1-3'A) which have been associated with slower disease progression. HIV-1 was recovered from seven of the eight, and recovered virus was used for sequencing the full-length HIV-1 genome; full-length HIV-1 genome sequences from the eighth were determined following amplification of viral sequences directly from peripheral blood mononuclear cells (PBMC). Longitudinal studies of one individual with HIV-1 that consistently exhibited a slow/low growth phenotype revealed a single amino acid deletion in a conserved region of the gp41 transmembrane protein that was not seen in any of 131 envelope sequences in the Los Alamos HIV-1 sequence database. Genetic analysis also revealed that five of the eight individuals harbored HIV-1 with unusual 1- or 2-amino-acid deletions in the Gag sequence compared to subgroup B Gag consensus sequences. These deletions in Gag have either never been observed previously or are extremely rare in the database. Three individuals had deletions in ***Nef*** , and one had a 4-amino-acid insertion in Vpu. The unusual polymorphisms in Gag, Env, and ***Nef*** described here were also found in stored PBMC samples taken 3 to 11 years prior to, or in one case 4 years subsequent to, the time of sampling for the original sequencing. In all, seven of the eight individuals exhibited one or more unusual polymorphisms; a total of 13 unusual polymorphisms were documented in these seven individuals. These polymorphisms may have been present from the time of initial infection or may have appeared in response to immune surveillance or other selective pressures. Our results indicate that unusual, difficult-to-revert polymorphisms in HIV-1 can be found associated with slow progression or nonprogression in a majority of such cases.

L43 ANSWER 3 OF 20 AIDSLINE
1999:12856 Document No.: MED-99412351. Protection by live, ***attenuated*** simian immunodeficiency virus against heterologous challenge. Wyand M S; Manson K; Montefiori D C; Lifson J D; Johnson R P; ***Desrosiers R C*** . Primedica, Worcester, Massachusetts 01608, USA. JOURNAL OF VIROLOGY (1999). Vol. 73, No. 10, pp. 8356-63. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB We examined the ability of a live, ***attenuated*** deletion mutant of simian immunodeficiency virus (SIV), SIVmac239Delta3, which is missing ***nef*** and vpr genes, to protect against challenge by heterologous strains SHIV89.6p and SIVsmE660. SHIV89.6p is a pathogenic, recombinant SIV in which the envelope gene has been replaced by a human immunodeficiency virus type 1 envelope gene; other structural genes of SHIV89.6p are derived from SIVmac239. SIVsmE660 is an uncloned, pathogenic, independent isolate from the same primate lentivirus subgrouping as SIVmac but with natural sequence variation in all structural genes. The challenge with SHIV89.6p was performed by the intravenous route 37 months after the time of vaccination. By the criteria of CD4(+) cell counts and disease, strong protection against the SHIV89.6p challenge was observed in four of four vaccinated monkeys despite the complete mismatch of env sequences. However, SHIV89.6p infection was established in all four previously vaccinated monkeys and three of the four developed fluctuating viral loads between 300 and 10,000 RNA copy equivalents per ml of plasma 30 to 72 weeks postchallenge. When other vaccinated monkeys were challenged with SIVsmE660 at 28 months after the time of vaccination, SIV loads were lower than those observed in unvaccinated controls but the level of protection was less than what was observed against SHIV89.6p in these experiments and considerably less than the level of protection against SIVmac251 observed in previous experiments. These results demonstrate a variable level of vaccine protection by live, ***attenuated*** SIVmac239Delta3 against heterologous virus challenge and suggest that even live, ***attenuated*** vaccine approaches for AIDS will face significant hurdles in providing protection against the natural variation present in field strains of virus. The results further suggest that factors other than anti-Env immune responses can be principally responsible for the vaccine protection by live, ***attenuated*** SIV.

L43 ANSWER 4 OF 20 AIDSLINE
1999:1111 Document No.: MED-98390160. Protective immunity induced by live ***attenuated*** simian immunodeficiency virus. Johnson R P; ***Desrosiers R C*** . Division of Immunology, New England Regional Primate Research Center, Harvard Medical School, Southborough, MA 01772, USA. pjohnson@warren.med.harvard.edu. CURRENT OPINION IN IMMUNOLOGY (1998). Vol. 10, No. 4, pp. 436-43. Journal code: AH1. ISSN: 0952-7915. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Lack of information on the mechanisms of protective immunity to AIDS virus infection represents a major obstacle to the development of a rational strategy for an effective HIV vaccine. In macaques, immunization with live ***attenuated*** simian immunodeficiency viruses has induced the most potent protective immunity and continued study promises a better understanding of the nature of protective immune responses. Recent evidence supports involvement of both cytotoxic T lymphocytes and neutralizing antibodies in protective immunity against infection by simian immunodeficiency virus, but more detailed studies are needed to document their relative importance.

L43 ANSWER 6 OF 20 AIDSLINE

1998:4305 Document No.: MED-98105790. Identification of highly ***attenuated*** mutants of simian immunodeficiency virus. ***Desrosiers R C*** ; Lifson J D; Gibbs J S; Czajak S C; Howe A Y; Arthur L O; Johnson R P. New England Regional Primate Research Center, Harvard Medical School, Southborough, Massachusetts 01772-9102, USA. rdesrosi@warren.med.harvard.edu. JOURNAL OF VIROLOGY (1998). Vol. 72, No. 2, pp. 1431-7. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Deletion mutants of the pathogenic clone of simian immunodeficiency virus isolate 239 (SIVmac239) were derived that are missing ***nef*** , vpr, and upstream sequences (US) in the U3 region of the LTR (SIVmac239 delta3), ***nef*** , vpx, and US (SIVmac239 delta3x), and ***nef*** , vpr, vpx, and US (SIVmac239 delta4). These multiply deleted derivatives replicated well in the continuously growing CEMx174 cell line and were infectious for rhesus monkeys. However, on the basis of virus load measurements, strength of antibody responses, and lack of disease progression, these mutants were highly ***attenuated*** . Measurements of cell-associated viral load agreed well with assays of plasma viral RNA load and with the strengths of the antibody responses; thus, these measurements likely reflected the extent of viral replication in vivo. A derivative of SIVmac239 lacking vif sequences (SIVmac239 delta vif) could be consistently grown only in a vif-complementing cell line. This delta vif virus appeared to be very weakly infectious for rhesus monkeys on the basis of sensitive antibody tests only. The weak antibody responses elicited by SIVmac239 delta vif were apparently in response to low levels of replicating virus since they were not elicited by heat-inactivated virus and the anti-SIV antibody responses persisted for greater than 1 year. These results, and the results of previous studies, allow a rank ordering of the relative virulence of nine mutant strains of SIVmac according to the following order: delta vpr > delta vpx > delta vpr delta vpx approximately delta ***nef*** > delta3 > delta3x > or = delta4 > delta vif > delta5. The results also demonstrate that almost any desired level of ***attenuation*** can be achieved, ranging from still pathogenic in a significant proportion of animals (delta vpr and delta vpx) to not detectably infectious (delta5), simply by varying the number and location of deletions in these five loci.

L43 ANSWER 7 OF 20 AIDSLINE
1997:22956 Document No.: MED-97456541. Induction of vigorous cytotoxic T-lymphocyte responses by live ***attenuated*** simian immunodeficiency virus. Johnson R P; Glickman R L; Yang J Q; Kaur A; Dion J T; Mulligan M J; ***Desrosiers R C*** . Division of Immunology, New England Regional Primate Research Center, Harvard Medical School, Southborough, Massachusetts 01772, USA. pjohnson@warren.med.harvard.edu. JOURNAL OF VIROLOGY (1997). Vol. 71, No. 10, pp. 7711-8. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Although live ***attenuated*** vaccine strains of simian immunodeficiency virus (SIV) have proven highly effective in protecting macaques against challenge with pathogenic SIV strains, little is known about the mechanisms of protective immunity induced by these vaccines. We examined cytotoxic T-lymphocyte (CTL) responses against SIV in animals infected with SIVmac239delta ***nef*** (deficient in ***nef***) or SIVmac239delta 3 (deficient in ***nef*** , vpr, and upstream sequences in U3). To enhance detection of SIV-specific CTL activity, we stimulated peripheral blood mononuclear cells with autologous B-lymphoblastoid cell lines which had been infected with recombinant vaccinia viruses expressing SIV proteins and subsequently inactivated with psoralen and UV light. Animals chronically infected with SIV239delta ***nef*** or SIV239delta 3 mounted vigorous CTL responses against the SIV Gag and Env proteins.

This CTL activity was major histocompatibility class restricted and mediated by CD8+ T lymphocytes. CTL responses persisted at relatively high levels for more than 6 years after infection. Limiting dilution precursor frequency assays demonstrated that the frequency of SIV-specific CTLs was as high as 234 CTL precursors per 100,000 cells. Animals acutely infected with SIV239delta ***nef*** developed CTL activity by day 14 after infection, coincident with decreases in viral load. Animals acutely infected with SIV239delta 3 developed CTL responses within 4 weeks of infection. Thus, vaccination of juvenile or adult animals with SIV239delta ***nef*** or SIV239delta 3 results in the induction of a vigorous CTL response which arises early in the course of infection and persists for years after a single inoculation of virus.

L43 ANSWER 15 OF 20 AIDSLINE
1994:10336 Document No.: MED-94347456. Safety issues facing development of a live- ***attenuated*** , multiply deleted HIV-1 vaccine [letter]. ***Desrosiers R C*** . AIDS RESEARCH AND HUMAN RETROVIRUSES (1994). Vol. 10, No. 4, pp. 331-2. Journal code: ART. ISSN: 0889-2229. Pub. country: United States. Language: English.

L43 ANSWER 17 OF 20 AIDSLINE
1993:3109 Document No.: MED-93110356. Protective effects of a live ***attenuated*** SIV vaccine with a deletion in the ***nef*** gene [see comments]. Daniel M D; Kirchhoff F; Czajak S C; Sehgal P K; ***Desrosiers R C*** . New England Regional Primate Research Center, Harvard Medical School, Southborough, MA 01772. SCIENCE (1992). Vol. 258, No. 5090, pp. 1938-41. Journal code: UJ7. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB Vaccine protection against the human immunodeficiency virus (HIV) and the related simian immunodeficiency virus (SIV) in animal models is proving to be a difficult task. The difficulty is due in large part to the persistent, unrelenting nature of HIV and SIV infection once infection is initiated. SIV with a constructed deletion in the auxiliary gene ***nef*** replicates poorly in rhesus monkeys and appears to be nonpathogenic in this normally susceptible host. Rhesus monkeys vaccinated with live SIV deleted in ***nef*** were completely protected against challenge by intravenous inoculation of live, pathogenic SIV. Deletion of ***nef*** or of multiple genetic elements from HIV may provide the means for creating a safe, effective, live ***attenuated*** vaccine to protect against acquired immunodeficiency syndrome (AIDS).

L43 ANSWER 18 OF 20 AIDSLINE
1993:2923 Document No.: MED-93103841. HIV with multiple gene deletions as a live ***attenuated*** vaccine for AIDS. ***Desrosiers R C*** . New England Regional Private Research Center, Harvard Medical School, Southborough, MA 01772-9102. AIDS RESEARCH AND HUMAN RETROVIRUSES (1992). Vol. 8, No. 8, pp. 1457. Journal code: ART. ISSN: 0889-2229. Pub. country: United States. Language: English.

L43 ANSWER 19 OF 20 AIDSLINE
1992:6989 Document No.: MED-92239218. HIV with multiple gene deletions as a live ***attenuated*** vaccine for AIDS. ***Desrosiers R C*** . New England Regional Primate Research Center, Harvard Medical School, Southborough, MA 01772-9102. AIDS RESEARCH AND HUMAN RETROVIRUSES (1992). Vol. 8, No. 3, pp. 411-21. Journal code: ART. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Most viral vaccines currently in use in humans are live ***attenuated*** strains of virus that lack pathogenic potential. In general, such live ***attenuated*** vaccines induce the strongest longest-lasting immunity.

Live ***attenuated*** strains of human immunodeficiency virus type 1 (HIV-1) have not been previously considered as vaccines for acquired immunodeficiency syndrome (AIDS) because of an inability to envision how their safety could be adequately assured. This report describes a means for making live, nonpathogenic strains of SIVmac and HIV-1 that cannot revert to a virulent form and a stepwise scheme for demonstrating their safety. Replication-competent, multiply deleted derivatives that are currently being tested are missing combinations of auxiliary genes (***nef*** , vpr, vif, vpx, vpu) and certain control elements in the negative regulatory element (NRE) of the long terminal repeat (LTR). Since these genomic regions are in large part conserved among the SIVs and HIVs, they are likely to be important for the virus life cycle in vivo. Consistent with this line of reasoning, a replication-competent ***nef*** deletion mutant of SIVmac apparently has lost most or all of its pathogenic potential, yet it still induces strong immune responses. Multiply deleted derivatives of SIVmac and HIV-1 will have to be extensively tested in animal models prior to moving a promising HIV-1 candidate to initial trials in high-risk human volunteers. Definitive evidence for safety and general acceptance for this approach can only evolve gradually over a prolonged period of time.

L43 ANSWER 20 OF 20 AIDSLINE
1991:6445 Document No.: MED-91235301. Importance of the ***nef*** gene for maintenance of high virus loads and for development of AIDS. Kestler H W 3d; Ringler D J; Mori K; Panicali D L; Sehgal P K; Daniel M D; ***Desrosiers R C*** . New England Regional Primate Research Center, Harvard Medical School, Southborough, Massachusetts 01772. CELL (1991). Vol. 65, No. 4, pp. 651-62. Journal code: CQ4. ISSN: 0092-8674. Pub. country: United States. Language: English.

AB When rhesus monkeys were infected with a form of cloned SIVmac239 having a premature stop signal at the 93rd codon of ***nef*** , revertants with a coding codon at this position quickly and universally came to predominate in the infected animals. This suggests that there are strong selective forces for open functional forms of ***nef*** in vivo. Although deletion of ***nef*** sequences had no detectable effect on virus replication in cultured cells, deletion of ***nef*** sequences dramatically altered the properties of virus in infected rhesus monkeys. Our results indicate that ***nef*** is required for maintaining high virus loads during the course of persistent infection in vivo and for full pathologic potential. Thus, ***nef*** should become a target for antiviral drug development. Furthermore, the properties of virus with a deletion in ***nef*** suggest a means for making live- ***attenuated*** strains of virus for experimental vaccine testing.

L48 ANSWER 1 OF 14 AIDSLINE
2000:15570 Document No.: MED-20307068. 1999: a time to re-evaluate AIDS vaccine strategies. ***Ruprecht R M*** ; Hofmann-Lehmann R; Rasmussen R A; Vlasak J; Xu W. Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts 02115, USA. ruth_ruprecht@dfci.harvard.edu. DA6 (2000). Vol. 3, No. 2, pp. 88-93. Journal code: DA6. ISSN: 1090-9508. Pub. country: United States. Language: English.

AB The field of AIDS vaccine development is in flux. Important new findings were reported in 1999 that led to a rethinking of AIDS vaccine strategies. We have been given the challenging task of providing an overview. Rather than attempting to provide a comprehensive summary, we will restrict our discussion to a few major topics, and we ask for understanding if we can only highlight.

L48 ANSWER 2 OF 14 AIDSLINE

2000:1756 Document No.: MED-20032582. Live attenuated AIDS viruses as vaccines: promise or peril?. ***Ruprecht R M*** . Dana-Farber Cancer Institute, Boston MA 02115-6084, USA. ruth_ruprecht@dfci.harvard.edu. IMMUNOLOGICAL REVIEWS (1999). Vol. 170, pp. 135-49. Journal code: GG4. ISSN: 0105-2896. Pub. country: Denmark. Language: English.

AB Live attenuated viruses can provide vaccine protection against various viral illnesses. A number of live attenuated strains of the simian immunodeficiency virus (SIV) or related lentiviruses have been evaluated in primate models as vaccine candidates against AIDS. Impressive efficacy was observed for some viruses, most notably SIV strains with deletions in the ***nef*** -gene. Sterilizing immunity was seen against homologous and heterologous virus challenge, against cell-free and cell-associated challenge, against intravenous and mucosal challenge, and against challenge as early as 3 weeks and as late as 2.25 years after just one immunization. However, these promising efficacy results are overshadowed by safety problems, such as reversion of the vaccine strain to a pathogenic virus encoding full-length ***nef*** or residual virulence of multiply deleted vaccine strains. Strategies aimed at decreasing the replicative capacity of ***nef*** -deleted vaccine strains to increase the safety profile have significantly curtailed vaccine efficacy. Nevertheless, studies of live attenuated vaccine strains should proceed and should focus on determining the correlates of vaccine protection and the molecular determinants for virulence and attenuation.

L48 ANSWER 3 OF 14 AIDSLINE
1999:10008 Document No.: MED-99292920. Persistent infection of rhesus macaques by the rev-independent ***Nef*** (-) simian immunodeficiency virus SIVmac239: replication kinetics and genomic stability. von Gegerfelt A S; Liska V; Ray N B; McClure H M; ***Ruprecht R M*** ; Felber B K. Human Retrovirus Pathogenesis Group, ABL-Basic Research Program, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, Maryland 21702, USA. JOURNAL OF VIROLOGY (1999). Vol. 73, No. 7, pp. 6159-65. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB We generated previously a ***Nef*** (-), replication-competent clone of SIVmac239 in which the Rev protein and the Rev-responsive element were replaced by the constitutive transport element (CTE) of simian retrovirus type 1 (A. S. von Gegerfelt and B. K. Felber, Virology 232:291-299, 1997). In the present report, we show that this virus was able to infect and replicate in rhesus macaques. The Rev-independent ***Nef*** (-) simian immunodeficiency virus induced a persistent humoral immune response in all monkeys, although viral loads were very low. Upon propagation in the monkeys, the genotype remained stable and the virus retained its in vitro growth characteristics. The infected monkeys showed normal hematological values and no signs of disease at more than 18 months post-virus exposure. Therefore, replacement of the essential Rev regulation by the CTE generated a virus variant that retained its replicative capacity both in vitro and in vivo, albeit at low levels.

L48 ANSWER 4 OF 14 AIDSLINE
1999:4271 Document No.: MED-99128058. Live attenuated, multiply deleted simian immunodeficiency virus causes AIDS in infant and adult macaques [see comments] [published erratum appears in Nat Med 199 May;5(5):590]. Baba T W; Liska V; Khimani A H; Ray N B; Dailey P J; Penninck D; Bronson R; Greene M F; McClure H M; Martin L N; ***Ruprecht R M*** . Dana-Farber Cancer Institute, Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115, USA. NATURE MEDICINE (1999). Vol. 5, No. 2, pp. 194-203. Journal code: CG5. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB A substantial risk in using live attenuated, multiply deleted viruses as vaccines against AIDS is their potential to induce AIDS. A mutant of the simian immunodeficiency virus (SIV) with large deletions in ***nef*** and vpr and in the negative regulatory element induced AIDS in six of eight infant macaques vaccinated orally or intravenously. Early signs of immune dysfunction were seen in the remaining two offspring. Prolonged follow-up of sixteen vaccinated adult macaques also showed resurgence of chronic viremia in four animals: two of these developed early signs of disease and one died of AIDS. We conclude that this multiply deleted SIV is pathogenic and that human AIDS vaccines built on similar prototypes may cause AIDS.

L48 ANSWER 5 OF 14 AIDSLINE
1998:7760 Document No.: AIDS-98929206. Replication of the Rev-independent ***nef*** (-) SIV in juvenile macaques. Felber B K; von Gegerfelt A S; Liska V; ***Ruprecht R M*** . NCI-FCRDC, National Institutes of Health, Frederick, MD. Conf Retroviruses Opportunistic Infect (1998). Vol. 5th, pp. 131 (Abstract No. 279). Pub. country: United States. Language: English.

AB All lentiviruses depend on the posttranscriptional regulation mediated by the viral Rev protein binding to the RRE located on a subset of viral mRNAs encoding the structural proteins. In contrast, type D retroviruses expression is mediated via cellular factor(s) interacting with the viral CTE, an RNA element with an extended stem-loop structure (1). In the presence of the positive acting factors, the RRE- and CTE-containing mRNAs are efficiently transported to the cytoplasm via distinct nuclear export pathways (2). To study the role of the Rev in virus propagation, we have generated Rev-independent clones of HIV and SIV and have demonstrated that the Rev/RRE system can be replaced by the CTE and generate infectious virus (3). The Rev-independent viruses have lower infectivity; lower replicative capacities in cultured PBMC; stable genotypes and stable in vitro attenuated growth properties. In SCID-hu mice, infection by these viruses results in reduced viral load and do not cause CD4 depletion (4). To test the in vivo properties, three juvenile macaques were injected intravenously with a Rev(-)RRE(-) ***Nef*** (-)CTE(+) SIVmac239. We show that this virus induced consistent, low-level infections. Analysis of cell-associated viral load and plasma RNA demonstrated that all monkeys are infected systemically. Starting 4 weeks post inoculation, they were also persistently Western blot positive. Upon propagation in monkeys, the genotype is stable and retained its in vitro characteristics. Since this virus variant lacks ***Nef*** , it is not expected to be pathogenic, and its ability to induce protection against wild type virus challenge will be tested The ability to express SIV independent of Rev may allow the generation of less pathogenic virus variants in vivo due to a change in the regulatory axis, which may result in an altered interaction with the host.

L48 ANSWER 6 OF 14 AIDSLINE
1997:10382 Document No.: AIDS-97920671. SIV neutralization. Montefiori D C; Baba T W; Robinson H L; Lu S; Hoxie J A; ***Ruprecht R M*** ; Hirsch V M. Duke University Medical Center, Durham, NC. Conf Adv AIDS Vaccine Dev (1996). pp. 40. Pub. country: United States. Language: English.

AB SIV infection and vaccination in rhesus monkeys is a valuable model for studying correlates of immunity but remarkably little is understood about SIV neutralization "in vitro". We have evaluated the neutralizing phenotype of commonly used, uncloned and molecularly cloned strains of SIV, under different assay conditions with mouse and macaque monoclonal antibodies, and with macaque sera generated by infection or vaccination. Most strains of SIV were either broadly sensitive or resistant to

neutralization by macaque antisera. Neutralization-sensitive strains could be further differentiated with type-specific, neutralizing monoclonal antibodies. Our results indicate that neutralization-resistant strains of SIV contain neutralizing epitopes that are immunogenic in macaques but are not exposed on native homologous virus particles "in vitro". Molecularly cloned SIV(mac239)/ ***nef*** -open was the most difficult to neutralize, even by autologous antisera, which raises the possibility that protection by live attenuated SIV vaccines in adult macaques was not dependent on neutralizing antibodies. Infection by pathogenic, molecularly cloned SIV(smE543-3) induced autologous and heterologous neutralizing antibody responses which closely paralleled acute primary HIV-1 infection, suggesting a strong resemblance to primary HIV-1 isolates. We advise that studies aimed at evaluating neutralizing antibodies as a correlate of SIV vaccine protection should utilize virus variants for "in vitro" assays that represent the neutralizing phenotype of the challenge stock. Additional studies are needed to determine whether the impact of neutralizing antibodies "in vivo" will depend on using a challenge stock that is sensitive to neutralization "in vitro". These results also begin to identify reagents that might be useful in the SIV/macaque model for studies that could lead to a better understanding of primary HIV-1 isolate neutralization and ways to overcome this potential obstacle to HIV-1 vaccine development.

L48 ANSWER 7 OF 14 AIDSLINE
1997:9488 Document No.: MED-97113343. Neutralizing and infection-enhancing antibody responses do not correlate with the differential pathogenicity of SIVmac239delta3 in adult and infant rhesus monkeys. Montefiori D C; Baba T W; Li A; Bilska M; ***Ruprecht R M*** . Department of Surgery, Duke University Medical Center, Durham, NC 27710, USA. JOURNAL OF IMMUNOLOGY (1996). Vol. 157, No. 12, pp. 5528-35. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Variants of SIV containing a deletion in the ***nef*** gene are attenuated in adult macaques, where they provide protection from challenge with pathogenic SIV, but the mechanism of protection remains unknown. One of these attenuated variants carrying deletions in ***nef*** , vpr, and NRE (SIVmac239delta3) was recently found to be pathogenic in infant macaques exposed to the virus at birth. We investigated whether inadequate or inappropriate antiviral humoral immune responses could explain why this virus causes disease in infant macaques. Plasma samples from four infants infected with SIVmac251 and five infants and two adults infected with SIVmac239delta3 were evaluated for neutralizing Abs to a laboratory-passaged stock of SIVmac251, an animal challenge stock of SIVmac239/ ***nef*** -open, and a stock of SIVmac239delta3 to which animals were exposed. Plasma samples were evaluated further for complement-mediated Ab-dependent enhancement (C'-ADE) of SIVmac239/ ***nef*** -open in vitro. High-titer neutralizing Abs to SIVmac251 were detected in plasma samples from adults and most infants within 3 to 5 wk of infection with either virus. Neutralizing Abs to SIVmac239/ ***nef*** -open and SIVmac239delta3 developed more slowly, being undetectable before 23 to 63 wk of infection. Timing, magnitude, and breadth of neutralizing Ab responses did not correlate with progression to disease or lack thereof and gave no indication of an impaired humoral immune response in infants. Furthermore, C'-ADE was detected equally in plasma samples from adults and infants. The results indicate that infection with SIVmac239delta3 causes disease in infant macaques despite their mounting of antiviral humoral immune responses comparable to those of adults.

L48 ANSWER 8 OF 14 AIDSLINE
1997:6699 Document No.: MED-97036686. "Attenuated" simian immunodeficiency virus in macaque neonates. ***Ruprecht R M*** ; Baba T W; Liska V;

Bronson R; Penninck D; Greene M F. Laboratory of Viral Pathogenesis, Harvard Medical School and Dana-Farber Cancer Institute, Boston, Massachusetts 02115, USA. AIDS RESEARCH AND HUMAN RETROVIRUSES (1996). Vol. 12, No. 5, pp. 459-60. Journal code: ART. ISSN: 0889-2229. Pub. country: United States. Language: English.

L48 ANSWER 9 OF 14 AIDSLINE
1996:4869 Document No.: MED-96175571. Attenuated HIV vaccine: caveats [letter; comment]. ***Ruprecht R M*** ; Baba T W; Liska V. SCIENCE (1996). Vol. 271, No. 5257, pp. 1790-2. Journal code: UJ7. ISSN: 0036-8075. Pub. country: United States. Language: English.

L48 ANSWER 10 OF 14 AIDSLINE
1995:10111 Document No.: MED-95326842. Attenuated vaccines for AIDS? [letter; comment]. ***Ruprecht R M*** ; Baba T W; Greene M F. LANCET (1995). Vol. 346, No. 8968, pp. 177-8. Journal code: L0S. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.

L48 ANSWER 11 OF 14 AIDSLINE
1995:6024 Document No.: MED-95199707. Pathogenicity of live, attenuated SIV after mucosal infection of neonatal macaques [see comments]. Baba T W; Jeong Y S; Pennick D; Bronson R; Greene M F; ***Ruprecht R M*** . Department of Pediatrics, Tufts University School of Medicine, Boston, MA 02111. SCIENCE (1995). Vol. 267, No. 5205, pp. 1820-5. Journal code: UJ7. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB Adult macaques do not develop disease after infection with a ***nef*** deletion mutant of the simian immunodeficiency virus (SIV) and are protected against challenge with pathogenic virus. This finding led to the proposal to use ***nef*** -deleted viruses as live, attenuated vaccines to prevent human acquired immunodeficiency syndrome (AIDS). In contrast, neonatal macaques developed persistently high levels of viremia after oral exposure to and SIV ***nef*** , vpr, and negative regulatory element (NRE) deletion mutant. Severe hemolytic anemia, thrombocytopenia, and CD4+ T cell depletion were observed, indicating that neither ***nef*** nor vpr determine pathogenicity in neonates. Because such constructs have retained their pathogenic potential, they should not be used as candidate live, attenuated virus vaccines against human AIDS.

L48 ANSWER 12 OF 14 AIDSLINE
1993:1990 Document No.: MED-93073804. Animal models for anti-AIDS therapy. Koch J A; ***Ruprecht R M*** . Laboratory of Viral Pathogenesis, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA. ANTIVIRAL RESEARCH (1992). Vol. 19, No. 2, pp. 81-109. Journal code: 6I7. ISSN: 0166-3542. Pub. country: Netherlands. Language: English.

AB Primate and non-primate species have been used to study the pathobiology of the simian immunodeficiency virus (SIV) and of the human immunodeficiency virus type 1 (HIV-1), respectively, and to develop new therapeutic regimes. Transgenic mice which express either the entire HIV-1 provirus or subgenomic fragments have been used to analyze viral gene products in vivo and may serve as models for the development of agents targeted to select viral functions. Chimeric mice which were created by transplanting human hematolymphoid cells into mice suffering from congenital severe combined immunodeficiency (scid/scid or so called SCID mice), can be infected with HIV-1 and allow one to study the entire HIV-1 replicative cycle. Type C murine leukemia virus models have been used to develop new prophylactic and therapeutic strategies but their use is restricted to the evaluation of select antiviral drug inhibition, targeted to retroviral genes common to both Lentivirinae and Oncovirinae. The role of various animal model systems in the development of anti-HIV-1 and

anti-AIDS therapies is summarized.

L48 ANSWER 13 OF 14 AIDSLINE
1992:2835 Document No.: MED-92102760. Serine phosphorylation-independent downregulation of cell-surface CD4 by ***nef*** . Gama Sosa M A; DeGasperi R; Kim Y S; Fazely F; Sharma P; ***Ruprecht R M*** . AIDS RESEARCH AND HUMAN RETROVIRUSES (1991). Vol. 7, No. 11, pp. 859-60. Journal code: ART. ISSN: 0889-2229. Pub. country: United States. Language: English.

L48 ANSWER 14 OF 14 AIDSLINE
1990:16610 Document No.: ICA6-20022790. The ***nef*** gene down-regulates HIV-1 production. Gama Sosa M A; DeGasperi R; Bernard L D; Hall J; Fazely F; ***Ruprecht R M*** . Harvard Medical School, Boston, MA, USA. Int Conf AIDS (1990). Vol. 6, No. 2, pp. 132 (Abstract No. F.A.227). Pub. country: United States. Language: English.

AB OBJECTIVE: To analyze the effect of the ***nef*** gene product on HIV-1 propagation. METHODS: Human adenocarcinoma (HeLa) and T-lymphoid (Jurkat) cells constitutively expressing the HIV-1 ***nef*** gene product were prepared by transduction with recombinant retroviruses. The resulting HeLa ***nef*** and Jurkat ***nef*** cells were tested for ***nef*** expression and for their ability to modulate the expression of the reporter gene chloramphenicol acetyltransferase (CAT) following transfection of pU3R-III CAT, a plasmid containing the CAT gene under the transcriptional control of the HIV-1 LTR U3R region. We also measured virus production after transfection of the infectious HIV-1 proviral clone pHXBc2 into ***nef*** -expressing cells, and in parallel, we tested the susceptibility of these cells to infection with cell-free virus particles. RESULTS: HeLa and Jurkat cells stably expressing the ***nef*** gene product down-regulated CAT expression following transient transfection of pU3R-III CAT and yielded markedly less virus after transfection of pHXBc2. Following infection with cell-free HIV-1 particles, the Jurkat ***nef*** cells produced significantly less virus as compared to infection of wild-type Jurkat cells. Jurkat cells expressing the highest levels of ***nef*** exhibited the lowest levels of CD4 receptors as measured by FACS. CONCLUSION: Human cells expressing the HIV-1 ***nef*** product down-regulated virus production. Furthermore, human T cells expressing ***nef*** had significantly lower levels of CD4 receptors on their cell surface. These results suggest that the HIV-1 ***nef*** gene product not only down-regulates HIV-1 replication, but also profoundly influences host cell CD4 receptor levels. These observations implicate the ***nef*** product as an important factor in the regulation of HIV-1 propagation.

L53 ANSWER 5 OF 46 AIDSLINE
2000:3773 Document No.: MED-20111559. New prospects for the development of a ***vaccine*** against ***human*** ***immunodeficiency*** ***virus*** type 1. An overview. Girard M; Habel A; Chanel C. Departement de virologie, Institut Pasteur, Paris, France. mgirard@pasteur.fr. COMPTES RENDUS DE L ACADEMIE DES SCIENCES. SERIE III, SCIENCES DE LA VIE (1999). Vol. 322, No. 11, pp. 959-66. Journal code: CA1. ISSN: 0764-4469. Pub. country: France. Language: English.

AB During the past few years, definite progress has been made in the field of ***human*** ***immunodeficiency*** ***virus*** type 1 (***HIV*** -1) vaccines. Initial attempts using envelope gp120 or gp140 from T-cell line-adapted (TCLA) ***HIV*** -1 strains to vaccinate chimpanzees showed that neutralizing antibody-based immune responses were protective against challenge with homologous TCLA virus strains or strains with low replicative capacity, but these neutralizing antibodies remained

inactive when tested on primary ***HIV*** -1 isolates, casting doubts on the efficacy of gp120-based vaccines in the natural setting. Development of a live ***attenuated*** simian immunodeficiency virus (SIV) ***vaccine*** was undertaken in the macaque model using whole live SIV bearing multiple deletions in the ***nef*** , vpr and vpx genes. This ***vaccine*** provided remarkable protective efficacy against wild-type SIV challenge, but the deletion mutants remain pathogenic, notably in neonate monkeys. Study of the mechanisms of protection in the SIV model unravelled the importance of the T-cell responses, whether in the form of cytotoxic T-lymphocyte (CTL) killing activity, or in that of antiviral factor secretion of cytokines, beta-chemokines and other unidentified antiviral factors by CD8+ T-cells. Induction of such a response is being sought at this time using various live recombinant virus vaccines, either poxvirus or alphavirus vectors or DNA vectors, which can be combined together or with a gp120/gp140 boost in various prime-boost combination strategies. New vectors include ***attenuated*** vaccinia virus NYVAC, modified vaccinia strain Ankara (MVA), Semliki Forest virus, Venezuelan equine encephalitis virus, and Salmonellas. Recent DNA prime-poxvirus boost combination regimens have generated promising protection results against SIV or SIV/ ***HIV*** (SHIV) challenge in macaque models. Emphasis is also put on the induction of a mucosal immune response, involving both a secretory IgA response and a mucosal CTL response which could constitute a 'first line of defence' in the vaccinated host. Finally, a totally novel ***vaccine*** approach based on the use of Tat or Tat and Rev antigens has been shown to induce efficient protection from challenge with pathogenic SIV or SHIV in vaccinated macaques. The only ***vaccine*** in phase 3 clinical trials in human volunteers is a gp120-based ***vaccine*** , AIDSVAX. A prime-boost combination of a recombinant canarypoxvirus and a subunit gp120 ***vaccine*** is in phase 2. Emphasis has been put recently on the necessity of testing prototype vaccines in developing countries using immunogens derived from local virus strains. Trial sites have thus been identified in Kenya, Uganda, Thailand and South Africa where phase I trials have begun or are expected to start presently.

L53 ANSWER 10 OF 46 AIDSLINE
1999:4106 Document No.: MED-99099001. Genetic instability of live, ***attenuated*** ***human*** ***immunodeficiency*** ***virus*** type 1 ***vaccine*** strains. Berkhout B; Verhoef K; van Wamel J L; Back N K. Department of Human Retrovirology, Academic Medical Center, University of Amsterdam, 1105 AZ Amsterdam, The Netherlands. b.berkhout@amc.uva.nl. JOURNAL OF VIROLOGY (1999). Vol. 73, No. 2, pp. 1138-45. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Live, ***attenuated*** viruses have been the most successful vaccines in monkey models of ***human*** ***immunodeficiency*** ***virus*** type 1 (***HIV*** -1) infection. However, there are several safety concerns about using such an anti- ***HIV*** ***vaccine*** in humans, including reversion of the ***vaccine*** strain to virulence and recombination with endogenous retroviral sequences to produce new infectious and potentially pathogenic viruses. Because testing in humans would inevitably carry a substantial risk, we set out to test the genetic stability of multiply deleted ***HIV*** constructs in perpetuated tissue culture infections. The Delta3 candidate ***vaccine*** strain of ***HIV*** -1 contains deletions in the viral long terminal repeat (LTR) promoter and the vpr and ***nef*** genes. This virus replicates with delayed kinetics, but a profound enhancement of virus replication was observed after approximately 2 months of culturing. Analysis of the revertant viral genome indicated that the three introduced deletions were maintained but a 39-nucleotide sequence was inserted in the

LTR promoter region. This insert was formed by duplication of the region encoding three binding sites for the Sp1 transcription factor. The duplicated Sp1 region was demonstrated to increase the LTR promoter activity, and a concomitant increase in the virus replication rate was measured. In fact, duplication of the Sp1 sites increased the fitness of the Delta3 virus (Vpr/ ***Nef*** /U3) to levels higher than that of the singly deleted DeltaVpr virus. These results indicate that deleted ***HIV*** -1 ***vaccine*** strains can evolve into fast-replicating variants by multiplication of remaining sequence motifs, and their safety is therefore not guaranteed. This insight may guide future efforts to develop more stable anti- ***HIV*** vaccines.

L53 ANSWER 11 OF 46 AIDSLINE
1999:3133 Document No.: MED-99102602. Strong ***human*** ***immunodeficiency*** ***virus*** (***HIV***)-specific cytotoxic T-lymphocyte activity in Sydney Blood Bank Cohort patients infected with ***nef*** -defective ***HIV*** type 1. Dyer W B; Ogg G S; Demoitie M A; Jin X; Geczy A F; Rowland-Jones S L; McMichael A J; Nixon D F; Sullivan J S. Australian Red Cross Blood Service-NSW, Sydney, New South Wales, Australia. wdyer@arcbs.redcross.org.au. JOURNAL OF VIROLOGY (1999). Vol. 73, No. 1, pp. 436-43. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Proposals for the use of live ***attenuated*** ***human*** ***immunodeficiency*** ***virus*** (***HIV***) type 1 (***HIV*** -1) as a ***vaccine*** candidate in humans have been based on the protection afforded by ***attenuated*** simian immunodeficiency virus in the macaque model. Although it is not yet known if this strategy could succeed in humans, a study of the Sydney Blood Bank Cohort (SBBC), infected with an ***attenuated*** ***HIV*** -1 quasispecies with natural ***nef*** and ***nef*** /long terminal repeat deletions for up to 17 years, could provide insights into the long-term immunological consequences of living with an ***attenuated*** ***HIV*** -1 infection. In this study, ***HIV*** -specific cytoxic T-lymphocyte (CTL) responses in an SBBC donor and six recipients were examined over a 3-year period with enzyme-linked immunospot, tetrameric complex binding, direct CTL lysis, and CTL precursor level techniques. Strong ***HIV*** -specific CTL responses were detected in four of seven patients, including one patient with an undetectable viral load. Two of seven patients had weak CTL responses, and in one recipient, no ***HIV*** -specific CTLs were detected. High levels of circulating effector and memory ***HIV*** -specific CTLs can be maintained for prolonged periods in these patients despite very low viral loads.

L53 ANSWER 18 OF 46 AIDSLINE
1998:14266 Document No.: MED-98362104. Regions of ***human*** ***immunodeficiency*** ***virus*** type 1 ***nef*** required for function in vivo. Aldrovandi G M; Gao L; Bristol G; Zack J A. University of Alabama at Birmingham AIDS Center, Birmingham, Alabama 35294, USA. JOURNAL OF VIROLOGY (1998). Vol. 72, No. 9, pp. 7032-9. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB In vivo studies in monkeys and humans have indicated that immunodeficiency viruses with ***Nef*** deleted are nonpathogenic in immunocompetent hosts, and this has motivated a search for live ***attenuated*** ***vaccine*** candidates. However, the mechanisms of action of ***Nef*** remain elusive. To define the regions of ***human*** ***immunodeficiency*** ***virus*** type 1 (***HIV*** -1) ***Nef*** which mediate in vivo pathogenicity, a series of mutated isogenic viruses were inoculated into human thymic implants in SCID-hu mice. Mutation of several regions, including the myristoylation site at

the second glycine and a region encompassing amino acids 41 through 49 of ***Nef*** , profoundly affected pathogenicity. Surprisingly, mutations of prolines in either of the two distant PXXP SH3 binding domains did not affect pathogenicity, indicating that these regions are not required for ***Nef*** activity in developing T-lineage cells. These data suggest that some functions of ***Nef*** described in vitro may not be relevant for in vivo pathogenicity.

L53 ANSWER 19 OF 46 AIDSLINE
1998:9190 Document No.: MED-98244593. Why do we not have'an ***HIV*** ***vaccine*** and how can we make one? [see comments]. Burton D R; Moore J P. Department of Immunology, The Scripps Research Institute, La Jolla, California 92037, USA. burton@scripps.edu. NATURE MEDICINE (1998). Vol. 4, No. 5 Suppl, pp. 495-8. Journal code: CG5. ISSN: 1078-8956. Pub. country: United States. Language: English.

L53 ANSWER 23 OF 46 AIDSLINE
1998:1815 Document No.: MED-98101367. SIV ***vaccine*** for AIDS [letter; comment]. Farthing C F; Sullivan J L. SCIENCE (1998). Vol. 279, No. 5347, pp. 14-5. Journal code: UJ7. ISSN: 0036-8075. Pub. country: United States. Language: English.

L55 ANSWER 2 OF 6 AIDSLINE
1998:14463 Document No.: MED-98378043. In vivo resistance to simian immunodeficiency virus superinfection depends on attenuated virus dose. Cranage M P; Sharpe S A; ***Whatmore A M*** ; Polyanskaya N; Norley S; Cook N; Leech S; Dennis M J; Hall G A. Centre for Applied Microbiology and Research, Porton Down, Salisbury, UK. martin.cranage@camr.org.uk. JOURNAL OF GENERAL VIROLOGY (1998). Vol. 79, Pt. 8, pp. 1935-44. Journal code: I9B. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Infection of macaques with attenuated simian immunodeficiency virus (SIV) induces potent superinfection resistance that may be applicable to the development of an AIDS vaccine but little information exists concerning the conditions necessary for the induction of this vaccine effect. We report that only a high dose of attenuated SIVmac protected macaques against intravenous challenge with more virulent virus 15 weeks after primary infection. Three of four animals given 2000-20000 TCID50 of SIVmacC8, a molecular clone of SIVmac251(32H) with a 12 bp deletion in the nef gene, essentially resisted superinfection with uncloned SIVmac. In two animals challenge virus was never detected by PCR and in one animal challenge virus was detected on one occasion only. Although animals given 2-200 TCID50 of attenuated virus were superinfected they were spared from the loss of CD4 cells seen in infected naive controls. Protection from superinfection did not correlate with immune responses, including the levels of virus-specific antibodies or virus-neutralizing activity measured on the day of challenge; although, after superinfection challenge, Nef-specific CTL responses were detected only in animals infected with high doses of attenuated SIV. Unexpectedly, cell-associated virus loads 2 weeks after inoculation were significantly lower in animals infected with a high dose of attenuated SIV compared to those in animals infected with a low dose. Our results suggest that the early dynamics of infection with attenuated virus influence superinfection resistance.

L55 ANSWER 3 OF 6 AIDSLINE
1997:21119 Document No.: MED-97410274. Macaques infected with attenuated simian immunodeficiency virus resist superinfection with virulence-revertant virus. Sharpe S A; ***Whatmore A M*** ; Hall G A; Cranage M P. Centre for Applied Microbiology and Research, Porton Down, Salisbury, UK. JOURNAL OF GENERAL VIROLOGY (1997). Vol. 78, Pt. 8, pp.

1923-7. Journal code: I9B. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Macaques infected with attenuated simian immunodeficiency virus (SIVmac) can resist superinfection challenge with virulent virus, showing the potential of live attenuated virus as an AIDS vaccine. Superinfection resistance does not, however, prevent the generation of virulent virus in vivo, suggesting that such virus may circumvent the resistance effect. Here, we show that three macaques already infected with the attenuated molecular clone SIVmacC8 were resistant to superinfection with virulent virus that arose in vivo following repair of a 12 bp attenuating lesion in the nef/3' LTR. In contrast, four naive animals became infected following inoculation with blood taken from the macaque in which virulent virus arose. Loss of nef-specific cytotoxic T lymphocyte (CTL) responses followed repair of the attenuating lesion within nef in the donor animal, suggesting the possibility of escape from CTL-driven selection pressure.

L55 ANSWER 6 OF 6 AIDSLINE
1995:10379 Document No.: MED-95333295. Repair and evolution of nef in vivo modulates simian immunodeficiency virus virulence. ***Whatmore A M*** ; Cook N; Hall G A; Sharpe S; Rud E W; Cranage M P. Centre for Applied Microbiology and Research, Wiltshire, United Kingdom. JOURNAL OF VIROLOGY (1995). Vol. 69, No. 8, pp. 5117-23. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Experimental evidence from the simian immunodeficiency virus (SIV) model of AIDS has shown that the nef gene is critical in the pathogenesis of AIDS. Consequently, nef is of considerable interest in both antiviral drug and vaccine development. Preliminary findings in two rhesus macaques indicated that a deletion of only 12 bp found in the overlapping nef/3' long terminal repeat (LTR) region (9501 to 9512) of the SIVmacC8 molecular clone was associated with reduced virus isolation frequency. We show that this deletion can be repaired in vivo by a sequence duplication event and that sequence evolution continues until the predicted amino acid sequence of the repair is virtually indistinguishable from that of the virulent wild type. These changes occurred concomitantly with reversion to virulence, evidenced by a high virus isolation frequency and load, decline in anti-p27 antibody, substantial reduction in the CD4/CD8 ratio, and development of opportunistic infections associated with AIDS. These findings clearly illustrate the capacity for repair of small attenuating deletions in primate lentiviruses and also strongly suggest that the region from 9501 to 9512 in the SIV nef/3' LTR region is of biological relevance. In addition, the ability of attenuated virus to revert to virulence raises fundamental questions regarding the nature of superinfection immunity.

L61 ANSWER 4 OF 21 AIDSLINE
2000:4572 Document No.: MED-20087006. Partial "repair" of defective ***NEF*** genes in a long-term nonprogressor with human immunodeficiency virus type 1 infection. Carl S; Daniels R; Iafrate A J; Easterbrook P; Greenough T C; Skowronski J; ***Kirchhoff F*** . Institute for Clinical Virology, University of Erlangen-Nurnberg, Erlangen, Germany. JOURNAL OF INFECTIOUS DISEASES (2000). Vol. 181, No. 1, pp. 132-40. Journal code: IH3. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB A 36-bp deletion close to the 5' end of ***NEF*** that impaired ***Nef*** function was found in a long-term nonprogressor with human immunodeficiency virus type 1 (HIV-1) infection. Forms containing an adjacent duplication of 33 bp were also frequently observed. The duplication showed no homology to the deleted region but restored the overall length of the first variable loop of ***Nef*** . ***NEF***

alleles carrying the duplication were active in class I major histocompatibility complex (MHC-I) down-modulation and enhancement of virus infectivity. However, they showed little activity in CD4 down-regulation and were unable to stimulate viral replication in human peripheral blood mononuclear cells. Our study indicates that the enhancement of virion infectivity and the stimulation of HIV-1 replication in lymphocytes are distinct functions of ***Nef*** . Our findings also illustrate the capacity for repair of attenuating deletions in HIV-1 infection and suggest that a selective pressure for ***Nef*** -mediated MHC-I down-modulation and/or enhancement of virion infectivity exists.

L63 ANSWER 1 OF 1 AIDSLINE
1995:4722 Document No.: MED-95074932. ***Characterization*** of ***nef*** ***sequences*** in long-term survivors of ***human*** ***immunodeficiency*** ***virus*** type 1 infection. Huang Y; Zhang L; Ho D D. Aaron Diamond AIDS Research Center, New York University School of Medicine, New York 10016. JOURNAL OF VIROLOGY (1995). Vol. 69, No. 1, pp. 93-100. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Studies with the simian immunodeficiency virus have shown that nef deletion results in a low level of viremia and a lack of disease progression in monkeys. Given the similarity of this clinical profile to that observed in long-term survivors of ***human*** ***immunodeficiency*** ***virus*** type 1 (***HIV*** -1) infection, we sought to examine the nef gene in 10 patients who are clinically healthy and immunologically normal despite 12 to 15 years of infection. PCR and DNA sequencing were used to determine nef sequences in peripheral blood mononuclear cells obtained from long-term survivors. We found that there is no gross deletion within nef in the cases studied; most nef sequences (91.1%) obtained from 10 subjects contained a full-length and intact open reading frame. In addition, at the protein level, there were no discernible differences between the Nef consensus sequences derived from long-term survivors and those from patients with AIDS. We therefore conclude that deletion of or gross sequence abnormality within nef is not likely to be a common explanation for the well-being of long-term survivors of ***HIV*** -1 infection. Moreover, phylogenetic analysis of nef sequences suggests that ***HIV*** -1 strains found in our study subjects do not have a common origin.

L66 ANSWER 1 OF 6 AIDSLINE
1997:11643 Document No.: MED-97167516. Identification of HIV-1 determinants for replication in vivo. Su L; Kaneshima H; Bonyhadi M L; Lee R; Auten J; Wolf A; Du B; Rabin L; Hahn B H; ***Terwilliger E*** ; Mccune J M. HIV Group, SyStemix, Inc., 1501 California Avenue, Palo Alto, California, 94304, USA. lsu@med.unc.edu. VIROLOGY (1997). Vol. 227, No. 1, pp. 45-52. Journal code: XEA. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB Pathogenic organisms are frequently attenuated after long-term culture in vitro. The mechanisms of the attenuation process are not clear, but probably involve mutations of functions required for replication and pathogenicity in vivo. To identify these functions, a direct comparison must be made between attenuated genomes and those that remain pathogenic in vivo. In this study, we used the heterochimeric SCID-hu Thy/Liv mouse as an in vivo model to define human immunodeficiency virus type 1 (HIV-1) determinants which are uniquely required for replication in vivo. The Lai/IIIB isolate and its associated infectious molecular clones (e.g., HXB2) were found to infect T cell lines but failed to replicate in the SCID-hu Thy/Liv model. When a lab worker was accidentally infected by Lai/IIIB, however, HIV-1 was isolated only from infection of primary PBMC,

and not from infection of T cell lines. We hypothesized that the lab worker was exposed to a heterogeneous viral stock which had been attenuated by passage in immortalized T cell lines. Either a rare family member from this stock was selected for in vivo replication or, alternatively, an attenuated genotype dominant in vitro may have reverted to become more infectious in vivo. To address this hypothesis, we have used the SCID-hu Thy/Liv model to study the replication of HXB2 and of HXB2 recombinant viruses with HIV-1 fragments isolated from the infected lab worker. HXB2 showed no or very low levels of replication in the Thy/Liv organ. Replacement of its subgenomic fragment encoding the envelope gene with a corresponding fragment from the lab worker isolate generated a recombinant virus (HXB2/LW) which replicated actively in SCID-hu mice. The ***NEF*** mutation in the HXB2 genome is still present in HXB2/LW. Thus, the LW sequences encode HIV-1 determinants which enhance HIV replication in vivo in a ***NEF*** -independent mechanism. The specific determinants have been mapped to the V1-V3 regions of the HIV-1 genome. Six unique mutations in the V3 loop region of HXB2/LW have been identified which contribute to the increased replication in vivo.

L66 ANSWER 2 OF 6 AIDSLINE
1992:2021 Document No.: MED-92073409. Allelic variation in the effects of the ***nef*** gene on replication of human immunodeficiency virus type 1. ***Terwilliger E F*** ; Langhoff E; Gabuzda D; Zazopoulos E; Haseltine W A. Division of Human Retrovirology, Dana-Farber Cancer Institute, Boston, MA 02115. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA (1991). Vol. 88, No. 23, pp. 10971-5. Journal code: PV3. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The effects of the viral gene ***nef*** on human immunodeficiency virus type 1 (HIV-1) replication in culture were investigated using ***nef*** alleles of the HIV-1 IIIB and ELI strains. The results demonstrate significant allelic variation in the effect of ***nef*** on virus replication in both an established human CD4+ T-cell line and primary human lymphocytes. In the context of the HXB2 virus, the ELI ***nef*** allele but not the IIIB ***nef*** allele permits initiation of efficient low-multiplicity infection in primary peripheral blood mononuclear cells, including unfractionated peripheral blood lymphocytes, T cells, and monocyte/macrophages. Within the same genetic context, the IIIB ***nef*** allele slightly retards replication of the virus in a T-cell line, whereas the ELI ***nef*** allele accelerates replication of the virus. Sequences in the IIIB and ELI genomes outside of ***nef*** also moderate the effects of ***nef*** on HIV-1 replication. ***nef*** did not appear to determine the host-cell preference of the virus. These studies may help to reconcile apparently conflicting reports on the role of ***nef*** in HIV-1 replication and suggest that HIV-1 ***nef*** may play an important role in viral pathogenesis.

L68 ANSWER 2 OF 9 AIDSLINE
1997:11109 Document No.: MED-96407284. Predominance of defective proviral sequences in an HIV + long-term non-progressor. Schwartz D H; Viscidi R; Laeyendecker O; Song H; Ray S C; ***Michael N*** . Department of Molecular Microbiology and Immunology, Johns Hopkins School of Hygiene and Public Health, Baltimore, MD 21205, USA. IMMUNOLOGY LETTERS (1996). Vol. 51, No. 1-2, pp. 3-6. Journal code: GIH. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.

AB We examined the accessory genes and envelope V3 region of provirus obtained over a 5 year period from an HIV+ long-term non-progressor with very low viral load and no in vitro recoverable virus during that same time span. LTR sequences supported normal Tat-mediated promoter activity.

Multiple clones of ***nef*** sequences were highly conserved with < 10% containing frame shift or stop codon mutations. Functional analysis of the predominant ***nef*** sequence indicated wild type downregulation of surface CD4 and good function in a complementation infectivity assay. By contrast, inactivating mutations were found in 64% of amplicons containing vif, vpr, vpu, tat1, and rev1, and in 41% of amplicons containing env V3. Identical inactive sequences were obtained at an interval of 2 years, suggesting persistence of quiescent defective provirus in a long-lived clonal cell population. Furthermore, genetic distance versus time analysis revealed an absence of progressive evolution or arborization of quasispecies over time. This contrasts with data generated from other asymptomatic HIV+ individuals. The non-progressive pattern of env sequence diversity and low R2 for genetic divergence over time suggests that the defective provirus circulating in the periphery of this patient represents a randomly sampled 'fossil record' of earlier replication competent HIV-1 genomes.

L68 ANSWER 4 OF 9 AIDSLINE
1996:2761 Document No.: MED-96013770. Functional characterization of human immunodeficiency virus type 1 ***nef*** genes in patients with divergent rates of disease progression. ***Michael N L*** ; Chang G; d'Arcy L A; Tseng C J; Birx D L; Sheppard H W. Division of Retrovirology, Walter Reed Army Institute of Research, Rockville, Maryland 20850, USA. JOURNAL OF VIROLOGY (1995). Vol. 69, No. 11, pp. 6758-69. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB We have studied the sequence and function of the human immunodeficiency virus type 1 (HIV-1) ***nef*** genes from nine patients with highly divergent rates of disease progression enrolled in a longitudinal study of HIV disease. Over an average of 7.8 years of follow-up, three patients had net positive changes in CD4+ T-cell counts, three patients had net negative changes in CD4+ T cells but did not develop AIDS, and three patients progressed to AIDS. The ***nef*** gene from each of these patients was amplified and cloned, and the sequence of 8 to 10 clones was determined. Only 2 of 88 (2.3%) ***nef*** genes recovered from these nine patients were grossly defective. Moreover, there was no relationship between the phylogeny of ***nef*** sequences and the corresponding rates of disease progression from these patients. Representative ***nef*** genes from all nine patients were tested for their abilities to downregulate cell surface CD4 in a transient-transfection assay. There was no correlation found between the functions of the ***nef*** genes from these patients and their corresponding rates of disease progression. We conclude that the ***nef*** gene is not a common mediator of the rate of HIV disease progression in natural infection.

L68 ANSWER 7 OF 9 AIDSLINE
1995:8637 Document No.: MED-95287475. Defective accessory genes in a human immunodeficiency virus type 1-infected long-term survivor lacking recoverable virus. ***Michael N L*** ; Chang G; d'Arcy L A; Ehrenberg P K; Mariani R; Busch M P; Birx D L; Schwartz D H. Division of Retrovirology, Walter Reed Army Institute of Research, Rockville, MD 20850, USA. JOURNAL OF VIROLOGY (1995). Vol. 69, No. 7, pp. 4228-36. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB We have been studying a patient who acquired human immunodeficiency virus (HIV) infection via a blood transfusion 13 years ago. She has remained asymptomatic since that time. The blood donor and two other recipients have all died of AIDS. Although this patient has shown persistently strong seroreactivity to HIV type 1 (HIV-1) antigens by Western blot (immunoblot), she has been continually HIV culture negative in results

from multiple laboratories over the last 6 years and has a very low viral burden. Her CD4+ T-cell count has fluctuated around a mean of 399 cells per microliters, with little change in lymphocyte subset percentages. Strong cellular immune responses to HIV-1 epitopes by this patient have been demonstrated. We now report the results of an intensive molecular genetic analysis of the HIV-1 proviral quasispecies from this patient sampled over 5 years. Long terminal repeat region sequences supported the argument for normal basal and Tat-mediated promoter activities. Sequential sequencing of the ***nef*** gene revealed a low frequency (8.3%) of defective genes and a striking lack of sequence evolution. Functional analysis of predominant ***nef*** genes by both a cell surface CD4 downregulation and a viral infectivity complementation assay showed wild-type function. In contrast, sequential analysis of an amplicon containing the vif, vpr, vpu, tat1, and rev1 genes revealed the presence of inactivating mutations in 64% of the clones. These data suggest that this patient, initially infected with a virulent swarm of HIV-1, is presently infected with a more-attenuated viral quasispecies as a result of effective host immunity.

L68 ANSWER 9 OF 9 AIDSLINE
1992:2311 Document No.: MED-92085398. Viral DNA and mRNA expression correlate with the stage of human immunodeficiency virus (HIV) type 1 infection in humans: evidence for viral replication in all stages of HIV disease.
Michael N L ; Vahey M; Burke D S; Redfield R R. Department of Retroviral Research, Walter Reed Army Institute of Research, Rockville, Maryland 20850. JOURNAL OF VIROLOGY (1992). Vol. 66, No. 1, pp. 310-6. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Studies of cultivatable human immunodeficiency virus type 1 (HIV-1) from plasma samples from infected patients have shown a correspondence between increasing viral burden and disease progression, but these measurements are selective and thus nonrepresentative of the in vivo viral load. Quantitation of proviral DNA sequences by the polymerase chain reaction in purified CD4+ T cells has shown a similar relationship but does not provide a measure of viral gene expression. We have studied viral DNA, genomic RNA, and spliced mRNA expression of HIV-1 in infected patients with a quantitative polymerase chain reaction assay. Viral RNA expression is detected in all stages of infection. These data show that the natural history of HIV infection is associated with a shift in the balance of viral expression favoring the production of genomic RNA without a preceding period of true viral latency.